



Biopsia renale nel Diabete. indicazioni e risvolti terapeutici

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Diapositiva preparata da DOMENICO SANTORO e ceduta alla Società Italiana di Diabetologia.
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I° CONVEGNO NAZIONALE CONGIUNTO SIN - SID

La Malattia Renale Diabetica (DKD): Presente e Futuro dell'Approccio Integrato Nefro-
Diabetologico, Rimini 60° Congresso Nazionale SIN 2-5 Ottobre, 2019

Caucasian 59year old man

T2DM (ten years), with poor glycemic control (**HbA1c = 10.1%**) and **hypertension**.

Due to **RF with NS**: 24UrPr 2,3 gr; Cr Cl 35 ml/min, urin sed: negative, the patient was admitted to the Nephrology Unit.

Screening for autoimmunity, complement level, IFS and IFU and hepatitis were all negative

Caucasian 54year old woman

T2DM (five years) (**HbA1c = 6,4%**) with **hypertension; diabetic retinopathy**, cerebral ischemic episodes.

Two months before appearance of **RF and NS**: Proteinuria 24 h: 6951 mg; Clearance creatinina: 55 ml/min; urin sed: rare rbc Admission to the Nephrology Unit.

Screening for autoimmunity, complement level, IFS and IFU and hepatitis were all negative

Caucasian 63year old man

T2DM (seven years), (**HbA1c = 7,4%**), ischemic cardiopathy, **hypertension**.

Due to **NS** patient was admitted to the Nephrology Unit. (24h UPr 12 gr; Creat Cl 118 ml/min, hematuria 4-6 rc/hpf).

Screening for autoimmunity, complement level, IFS and IFU and hepatitis were all negative



Epidemiology

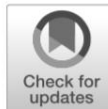


"25-33% of patients with T2DM have diabetic kidney disease"

"most common cause of ESRD"

Globally, the number of people with diabetes mellitus has quadrupled in the past three decades, and diabetes mellitus is the ninth major cause of death.

About 1 in 11 adults have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (T2DM).

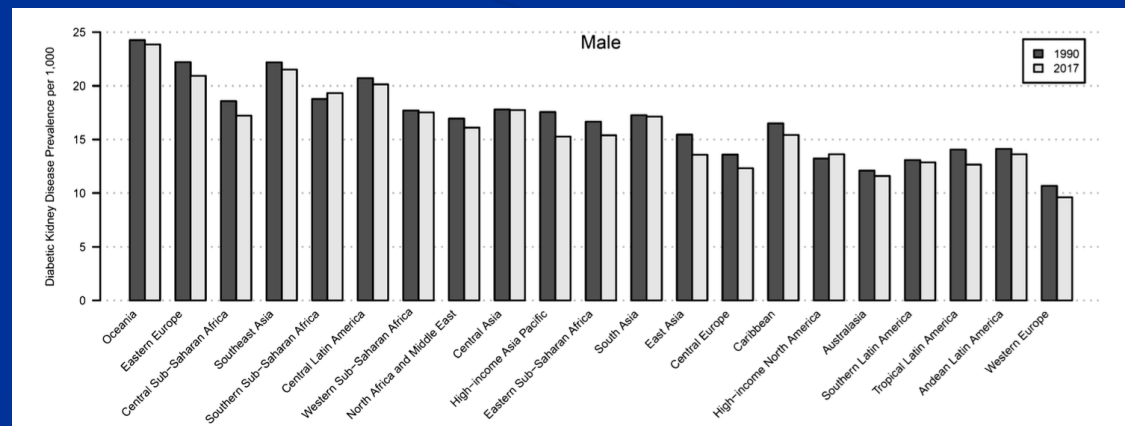
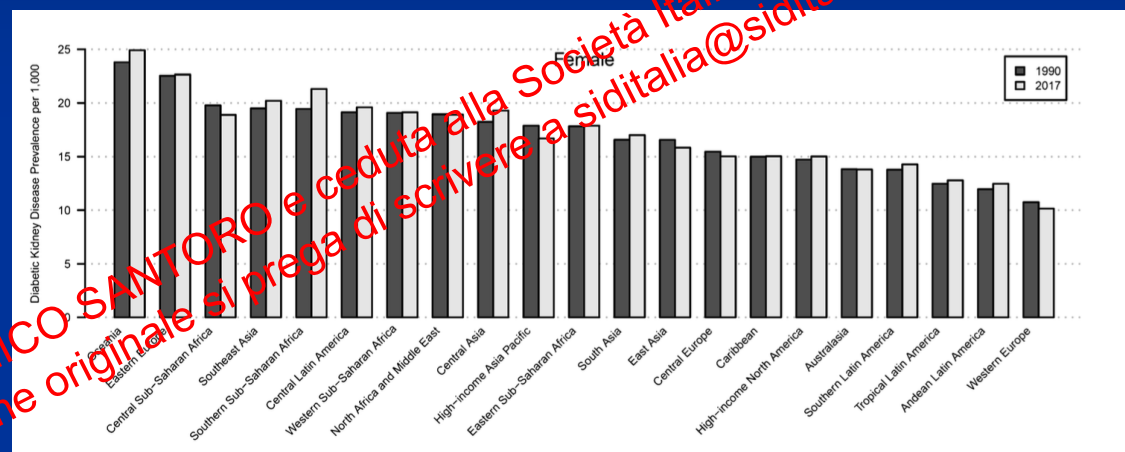


Diabetic Nephropathy

The Global Burden of Diabetic Kidney Disease: Time Trends and Gender Gaps

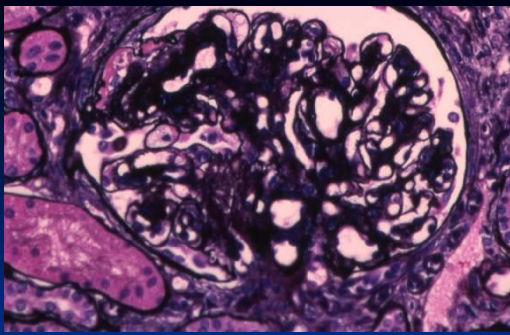
Bernadette Thomas¹

Global age-standardized prevalence of DKD in 1990 and in 2017:
men: 15.48/1000; women :16.50/1000

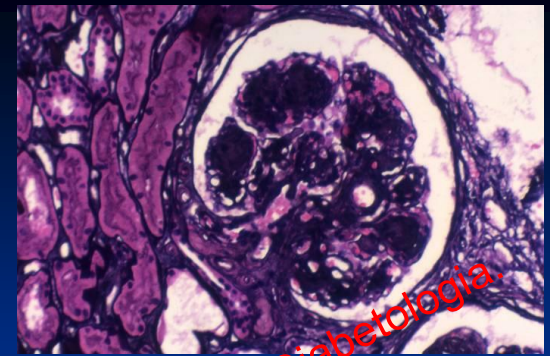


No difference between
1990 e 2017 in terms of
prevalence!!

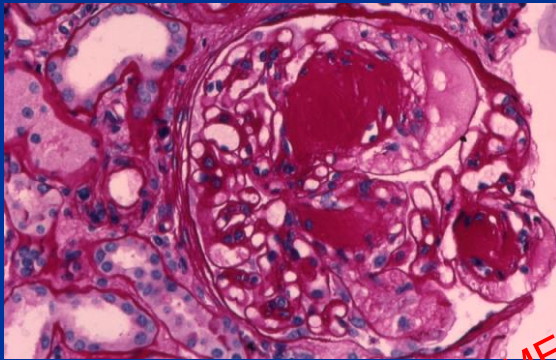
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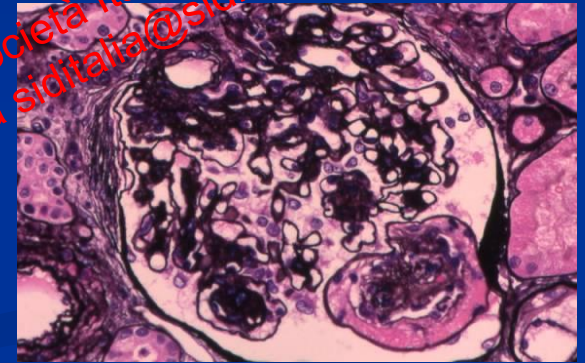
**DIFFUSE
MESANGIAL INCREASE**



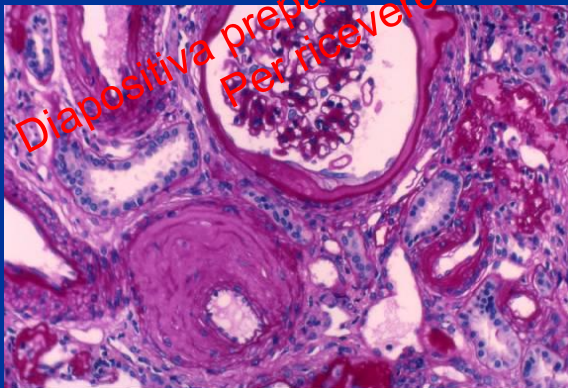
**NODULAR
MESANGIAL INCREASE**



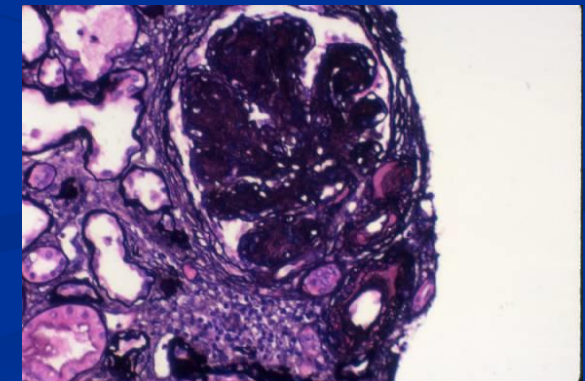
MICROANEURYSMS



MESANGIOLYSIS



AA INTIMAL FIBROSIS



**α IALINOSIS AT
VASCULAR POLE**

DIABETIC NEPHROPATHY

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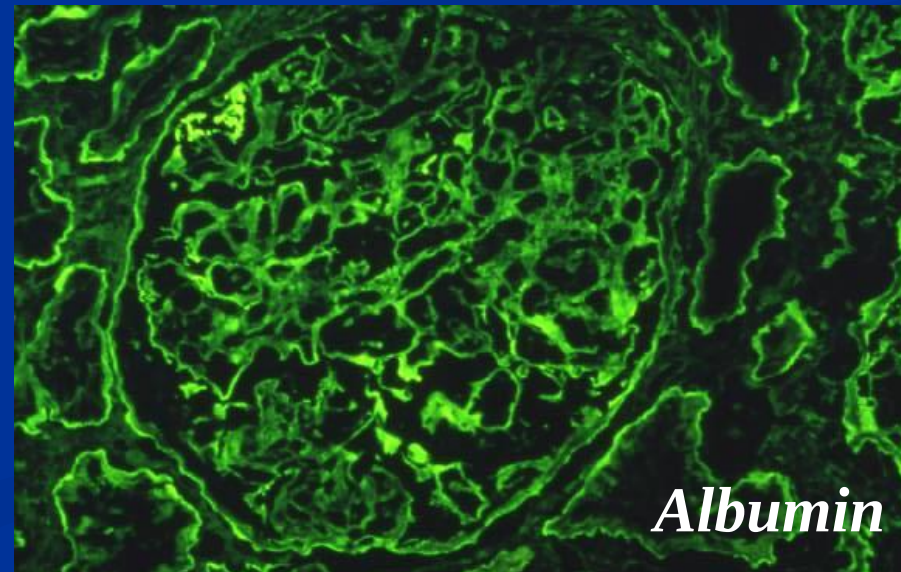
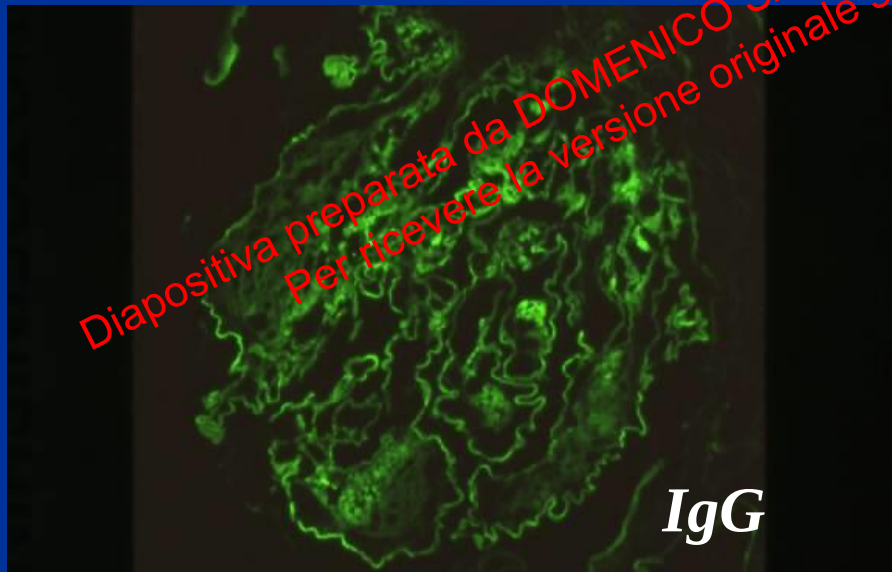
IMMUNOFLUORESCENCE

Findings

Linear staining of IgG and Albumin along the basement membranes of glomerulus, Bowman's capsule and tubules



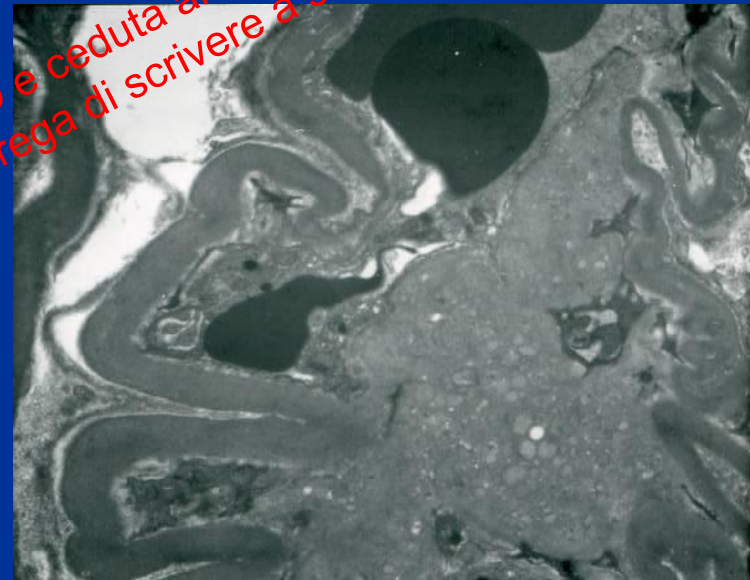
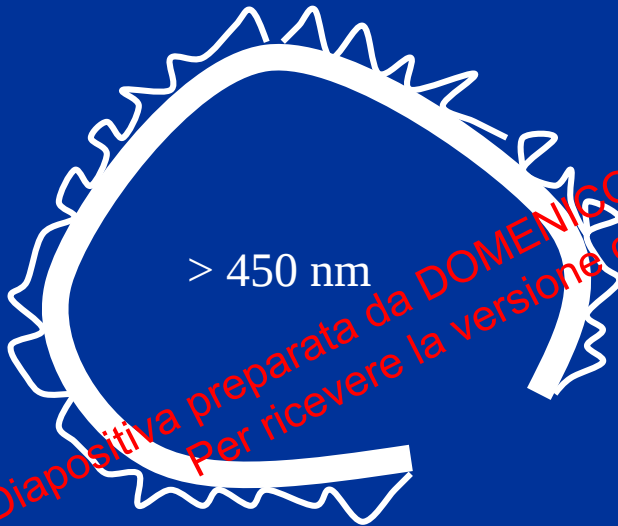
Change in the extracellular matrix of basement membranes which permits “trapping” of these serum proteins



GBM THICKENING

n.v. = 350-400 nm

The earliest change of DKD in patients
with DM ”



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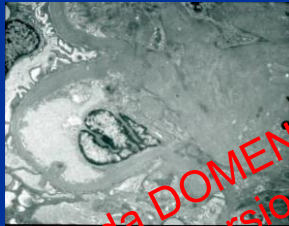
Pathogenesis of morphological damage in T1DM

METABOLIC ALTERATIONS



GBM
TBM
BC

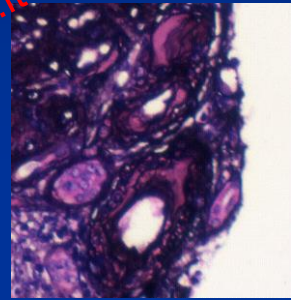
THICKENING



few years



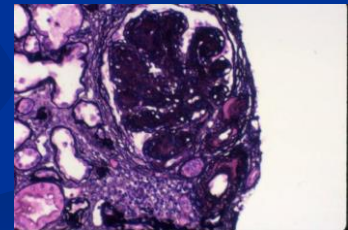
Afferent and
efferent
arteriolar
hyalinosis



5-7 ys



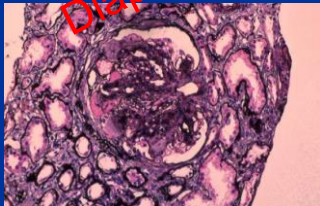
mesangial
widening



5-7 ys



nodular
glomerulosclerosis
tubular atrophy
interstitial fibrosis



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IDDM

Glomerulopathy
(microangiopathy)



vascular
tubular lesions
interstitial



GBM, TBM, BC Thickening
Mesangial widening



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NIDDM

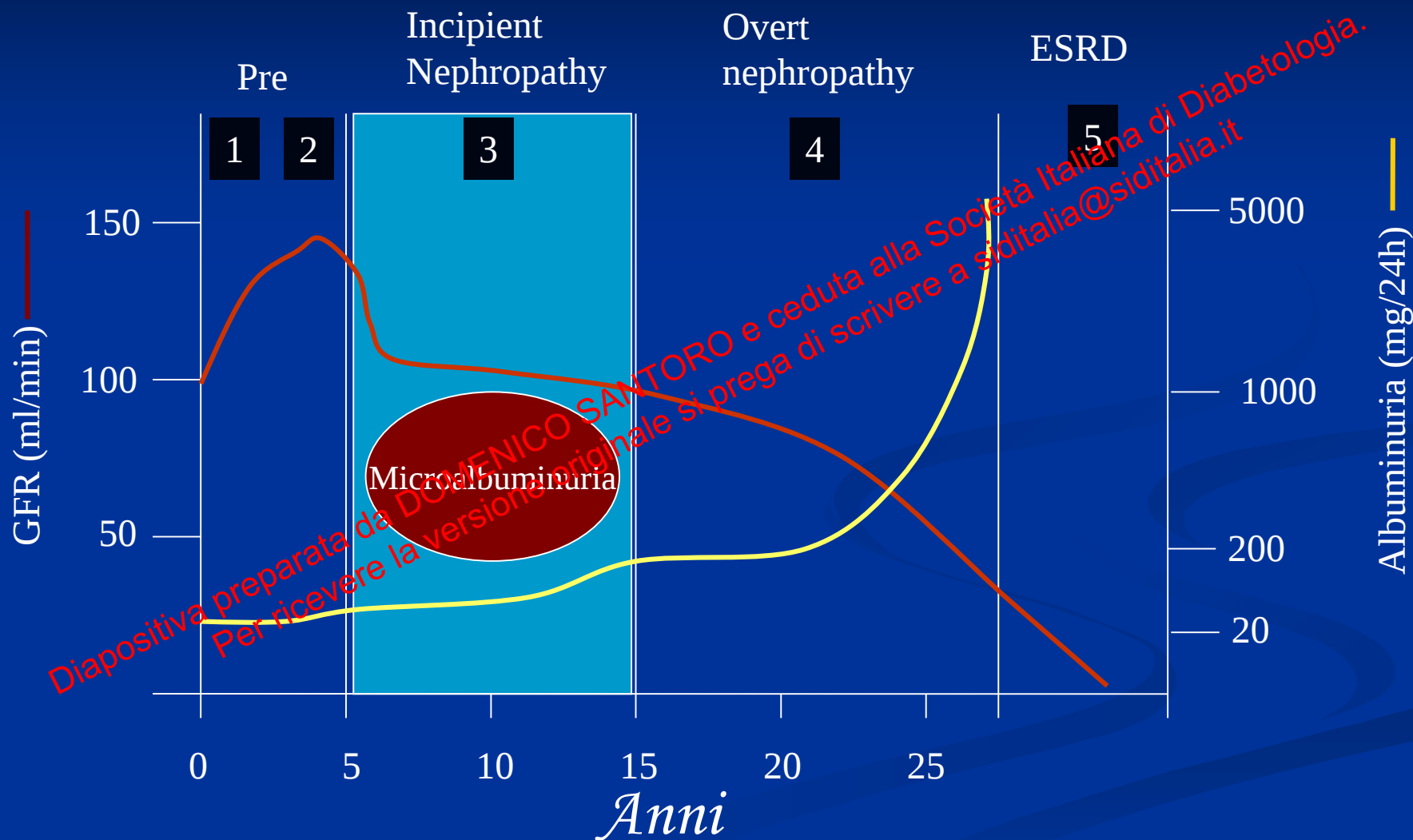


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Natural History of DKD



Is UAE always the first sign of DN ?



Is UAE always the first sign of DN ?

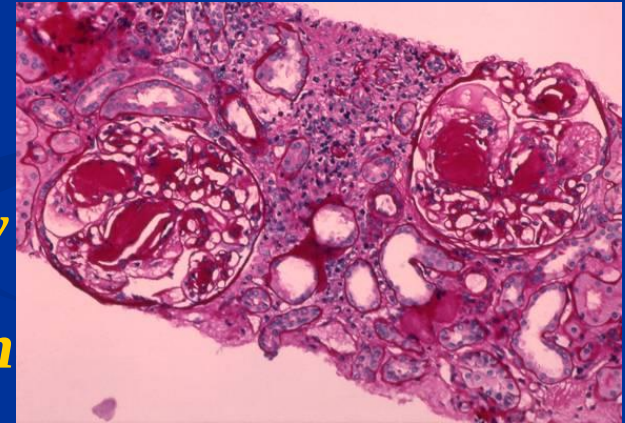
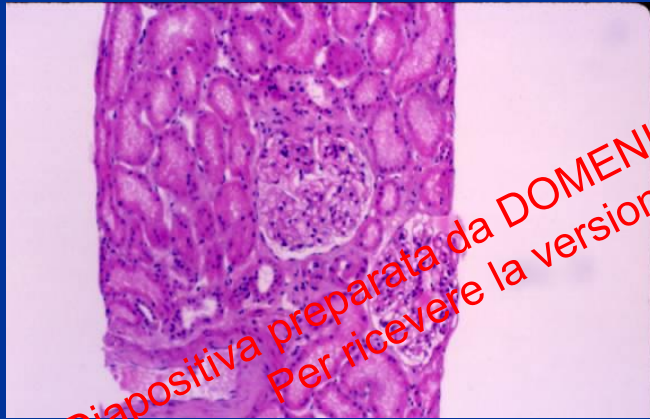
105 patients with **IDDM** (10 ys)

NORMOALBUMINURIC

GFR >90 ml/min
(121.2 ±16.6)

renal biopsies performed

GFR <90 ml/min
(75.9 ±11.7)



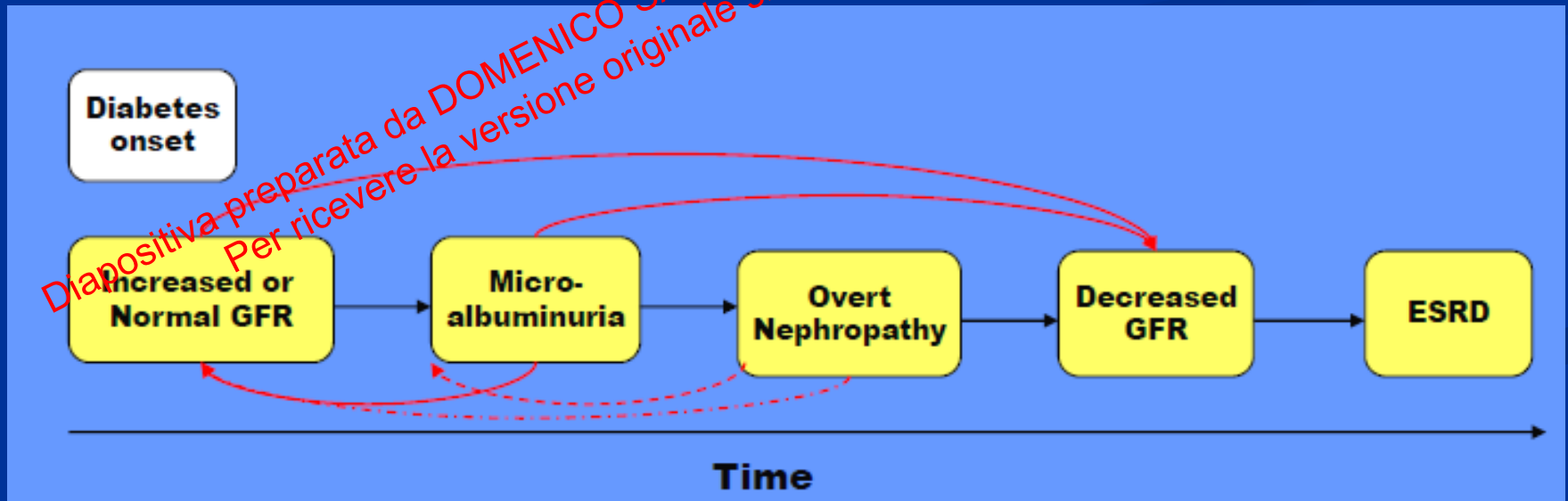
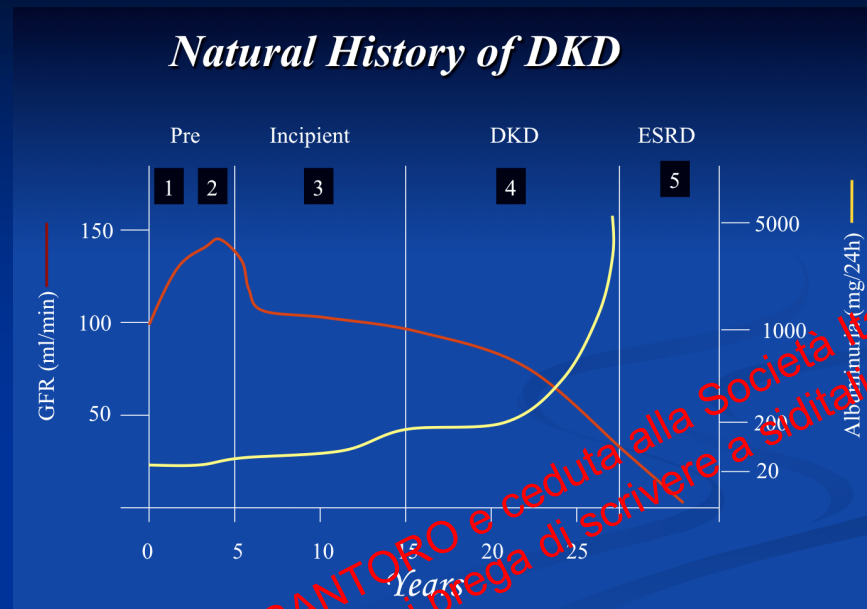
Female

Retinopathy

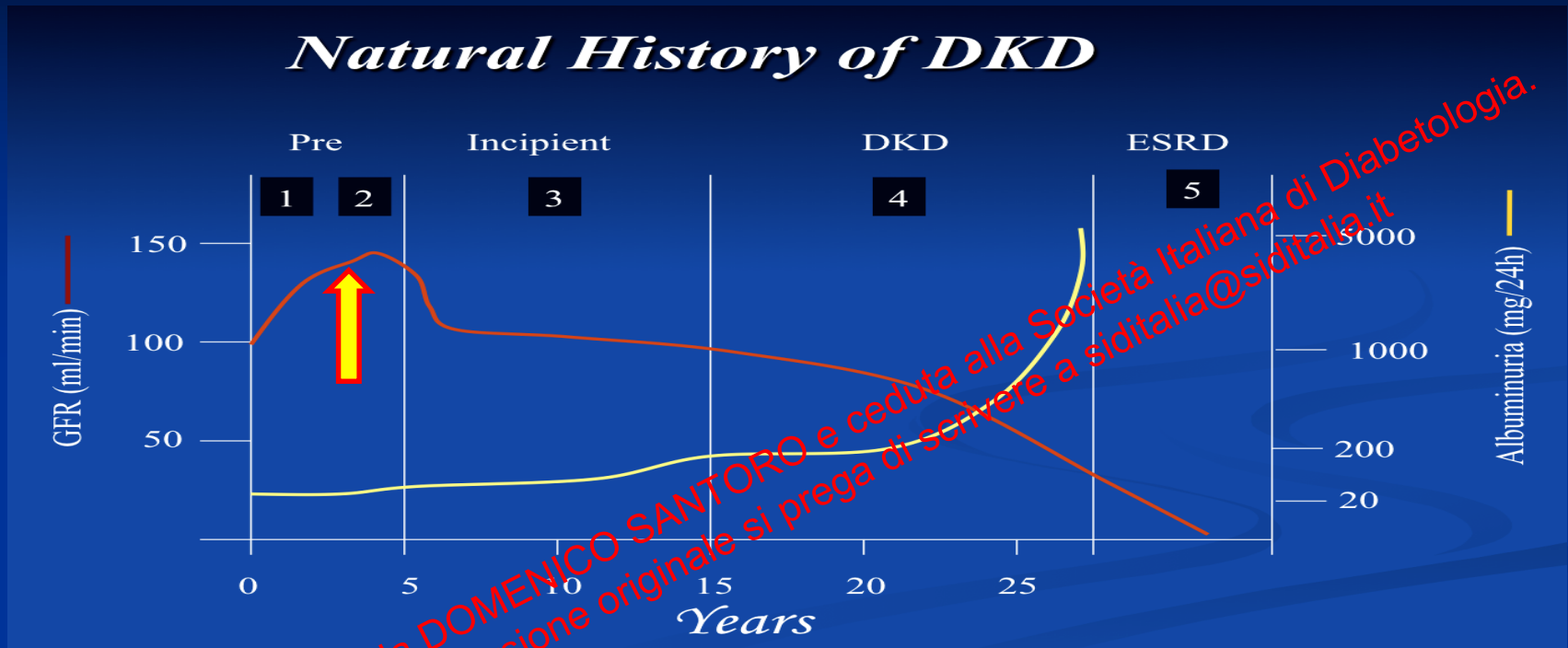
Hypertension

Regular measurements of GFR be performed in long-standing normoalbuminuric type 1 diabetic female diabetic patients, especially in those with retinopathy or hypertension

Natural History of Diabetic Nephropathy

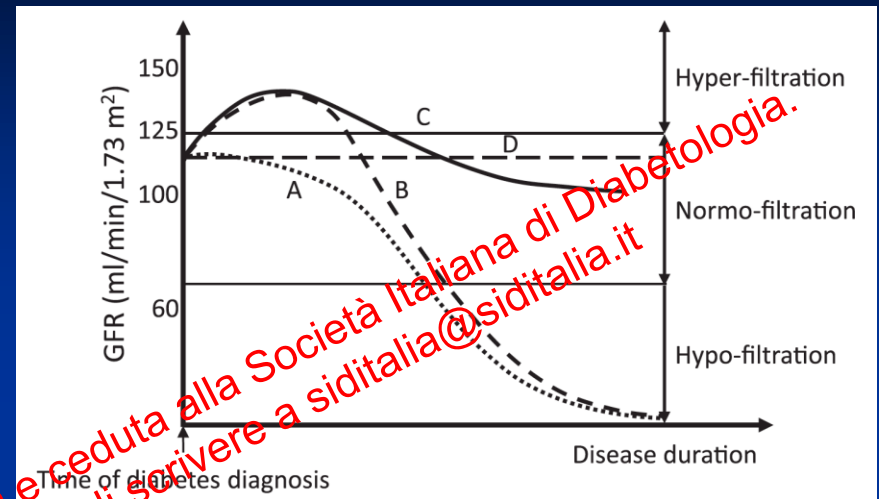
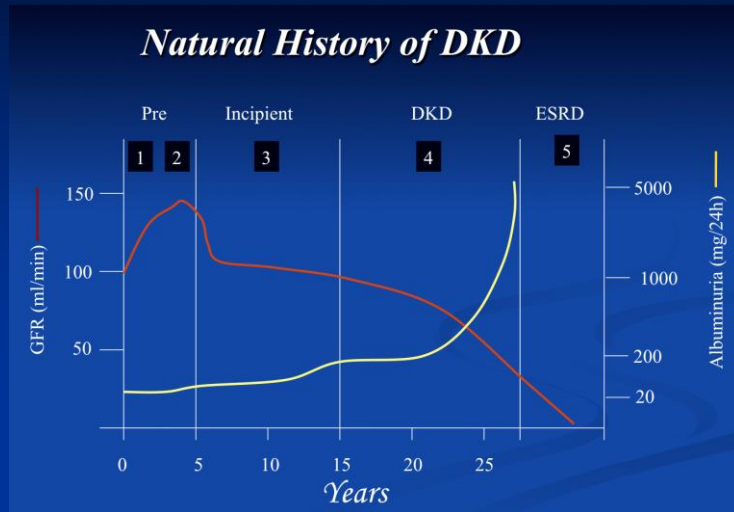


The role of hyperfiltration in DKD



Individuals with glomerular hyperfiltration were **at increased risk** of progression to diabetic nephropathy.

Hyperfiltration in Diabetic Nephropathy



The prevalence of hyperfiltration in type 1 diabetes varies from less than 25% to more than 75%. In type 2 diabetes, the prevalence is significantly lower, ranging between 0% and more than 40%.

Biological factors that may influence GFR in the hyperfiltration range include glucose control, diabetes duration, BMI, sex, pubertal status in type 1 diabetes and age in type 2 diabetes.

Clinical presentation

Diabetic patients with Proteinuria and/or Hematuria and/or low eGFR



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The prevalence of **non diabetic renal disease** varies from **12% to 79%**, depending on the **selection criteria** and the **population** being **studied**.

Clinical presentation

Diabetic patients with Proteinuria and/or Hematuria and/or low eGFR



Renal Biopsy

No Renal Biopsy

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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

- PubMed, Embase, CKNi: 1990-2012
- 26 studies (2.322 patients)

	DN	NDRD
Duration of DM	Longer	Shorter
Presence of Retinopathy	Yes (except 17,6%)	No (except 23,6%)
Blood pressure	Higher	Lower
HbA1c	Higher	Lower

No difference in:

- ages
- 24h Urinary protein
- Serum creatinine
- Clearance creatinine
- BUN

Retinopathy in DKD

Retinopathy
(microangiopathy)

86% microalbuminuric

99% proteinuric

T1DM

Retinopathy
(microangiopathy)

48% microalbuminuric

45% proteinuric

T2DM

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Hematuria in DKD

Authors	Year of publication	n	Patients with haematuria (%)	Definition of haematuria
O'Neill WM ¹	1983	30	9 (30.0%)	>10/hpf
Parving HH ³	1992	27	4 (14.8%)	≥3/hpf
Matsumae T ⁴	1994	162	40 (24.5%)	n.d.
Matsumura N ⁵	1994	143	15 (10.5%)	≥5/hpf
Tone A ⁶	2005	25	11 (44.0%)	>10/μL
Soni S ⁷	2006	44	4 (9.1%)	>3/hpf
Pham TT ⁸	2007	64	48 (75.0%)	≥2/hpf
Akimoto T ⁹	2008	34	14 (41.2%)	>10/hpf
Zhou J ¹⁰	2008	60	10 (16.7%)	n.d.
Lin YL ¹¹	2009	24	8 (33.3%)	>5/hpf
Mou S ¹²	2010	33	10 (30.3%)	≥2/hpf
Chang TI ¹³	2011	43	24 (55.8%)	>3/hpf
Chong YB ¹⁴	2012	69	28 (40.6%)	n.d.
Oh SW ¹⁵	2012	50	39 (78.0%)	≥5/hpf

Prevalence of microscopic haematuria in patients with biopsy-confirmed diabetic nephropathy

9.1-78%

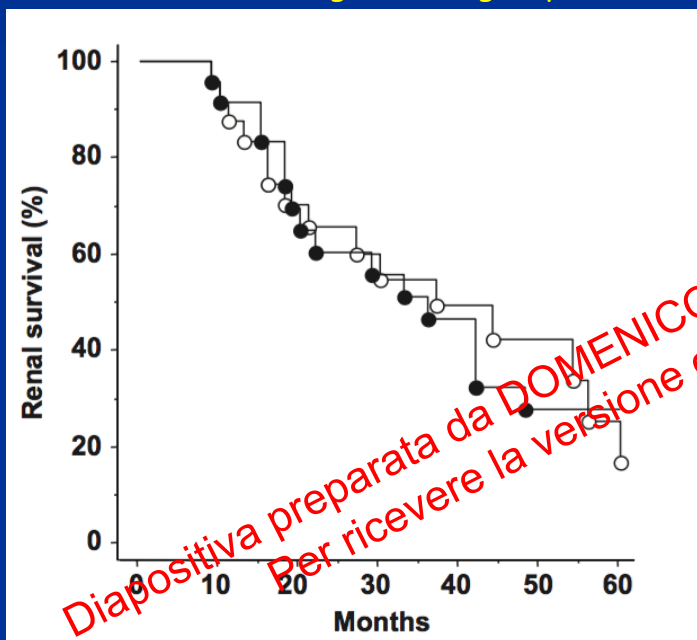
>3 - >10hpf

Hematuria in DKD

Eighty-four type 2 diabetes patients with overt proteinuria and biopsy-confirmed DN:

Patients with persistent haematuria (group 1) and with non-persistent haematuria (group 2)

Clinical findings of two groups



Renal survival rates in relation to persistent microscopic haematuria after renal biopsy

No difference.

Histological findings of pts with persistent microscopic haematuria

	Multivariate analysis OR (95% CI)	P-value
Diffuse lesion	1.55 (0.24–10.02)	0.64
Nodular lesion	0.23 (0.04–1.25)	0.09
Exudative lesion (yes/no)	0.38 (0.09–1.61)	0.19
Arteriolar hyalinosis	2.81 (1.03–7.70)	0.04
Interstitial fibrosis	0.57 (0.10–3.19)	0.52
Percentage of global glomerulo-sclerosis (%)	0.98 (0.94–1.02)	0.26

Hematuria in DKD



JDI

Journal of Diabetes Investigation
Official Journal of the Asian Association for the Study of Diabetes

Open access



ORIGINAL ARTICLE

Dysmorphic erythrocytes are superior to hematuria for indicating non-diabetic renal disease in type 2 diabetics

Zhe-yi Dong, Yuan-da Wang, Qiang Qiu, Kai Hou, Li Zhang, Jie Wu, Han-yu Zhu, Guang-yan Cai, Xue-feng Sun, Xue-guang Zhang, Mo-yan Liu, Jia Kou, Xiang-mei Chen*

Department of Nephrology, Chinese PLA General Hospital, Chinese PLA Institute of Nephrology, State Key Laboratory of Kidney Diseases, National Clinical Research Center of Kidney Diseases, Beijing, China

The Role of Dysmorphic Erythrocytes

198 patients with type 2 diabetes who underwent kidney biopsies between 2012 and 2013.

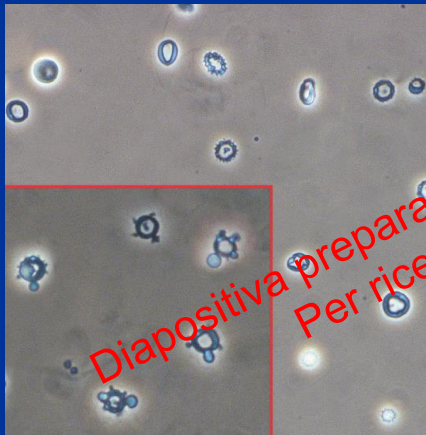


Table 2 | Comparison of the incidence of hematuria in the diabetic nephropathy and non-diabetic renal disease groups

Definition of hematuria (RBCs/hpf)	DN group, presence (%)	NDRD group, presence (%)	P-value
>2	24 (39.3%)	64 (46.7%)	0.29
>3	19 (31.1%)	60 (43.8%)	0.77
>5	15 (24.6%)	42 (30.7%)	0.33
>7	10 (16.4%)	31 (22.6%)	0.27
>8	7 (11.5%)	27 (19.7%)	0.13
>10	4 (6.6%)	23 (16.8%)	0.04
>15	3 (4.9%)	15 (10.9%)	0.17
Glomerular hematuria	2 (3.3%)	34 (24.8%)	<0.001

The Role of Dysmorphic Erythrocytes

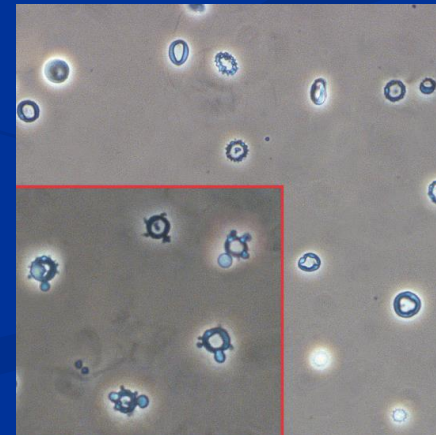
Three different definitions of **hematuria** in urine sediment. were used:

- **>3 RBCs/ hpf,**
- **>10 RBCs/hpf**
- **dysmorphic erythrocytes >80%**

Table 3 | Predictive value of three different diagnostic criteria for hematuria

	>3 RBCs/hpf	>10 RBCs/hpf	Glomerular hematuria
Sensitivity	0.44	0.17	0.25
Specificity	0.99	0.93	0.97
Positive predictive value	0.76	0.85	0.94
Negative predictive value	0.35	0.33	0.36
ROC AUC	0.57	0.56	0.61

If a patient had **glomerular hematuria**, the probability of **NDRD** was **94%**.
Conversely, the **rate of exclusion** of **NDRD** was **36%**



Indication for renal biopsy and Type of non-diabetic renal disease

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Type of NDRD

Single-center retrospective analysis based on medical records:

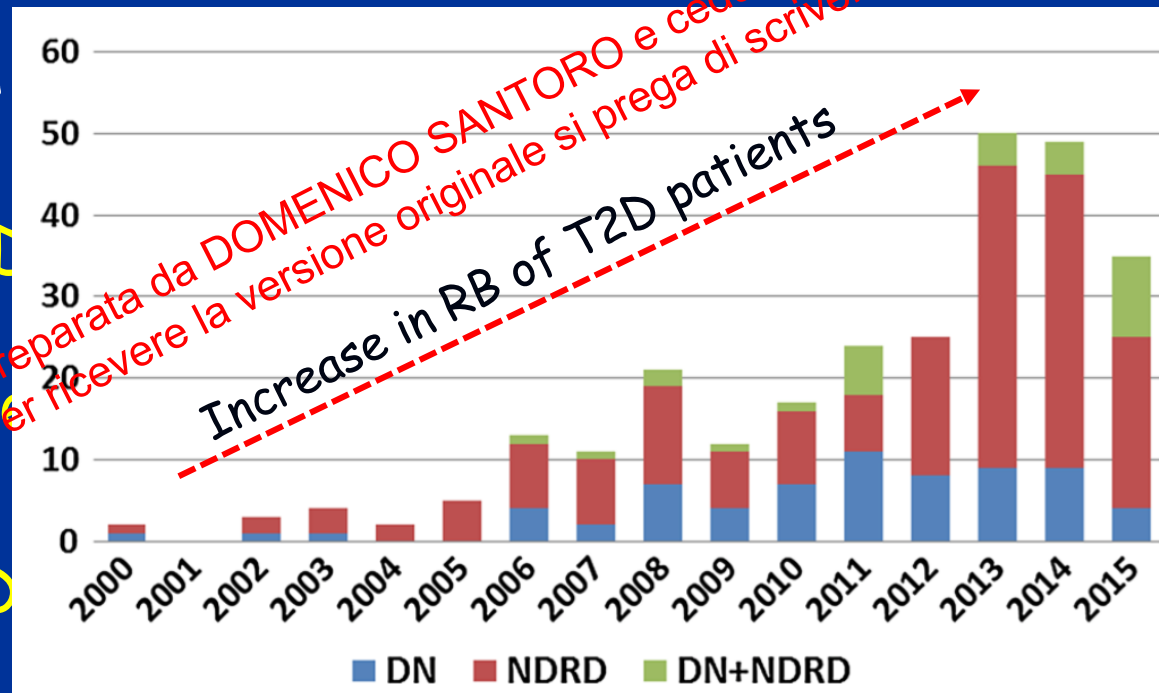
273 T2D patients (172 men, mean age: 51.1 ± 12.4 years) who underwent renal biopsy between February 2000 and October 2015.

Patients

➤ pure DN

➤ isolated NDRD

➤ NDRD



Type of NDRD

Pathologic diagnosis based on renal biopsy	NDRD (N = 175)	DN + NDRD (N = 30)	Total (N = 205)
Membranous nephropathy	52 (29.7)		58 (28.3)
IgA nephropathy	40 (22.9)		41 (20)
Mesangioproliferative glomerulonephritis (MPGN)	14 (8.0)		14 (6.8)
Minimal change disease	6 (3.4)		6 (2.9)
Crescentic glomerulonephritis	4 (2.3)		4 (2.0)
Focal segmental glomerulosclerosis	3 (1.7)		3 (1.5)
Interstitial nephritis	10 (5.7)		11 (5.4)
Lupus nephritis	9 (5.1)		9 (4.4)
HBV-associated glomerulonephritis	8 (4.6)		8 (3.9)
Hypertensive renal arteriolar sclerosis	6 (3.4)		25 (12.2)
ANCA-associated vasculitis	5 (2.9)		6 (2.9)
Thrombotic microangiopathy (TMA)	4 (2.3)		6 (2.9)
Amyloidosis	4 (2.3)		4 (2.0)
Henoch-Schonlein purpura	1 (0.6)		1 (0.5)
Lipoprotein glomerulopathy	1 (0.6)		1 (0.5)
Acute tubular necrosis	1 (0.6)		1 (0.5)
Others	7 (3.9)		7 (3.3)

Clinical signs of NDRD

Patients with NDRD

- Shorter duration of diabetes
- Lower diabetic retinopathy (DR, 6.9 %)
- Lower renal failure (28.0 %) and higher estimated glomerular filtration rates (eGFR)
- Lower systolic blood pressure (SBP)

No significant between-group differences were observed with respect to proteinuria and hematuria.

ORIGINAL ARTICLE

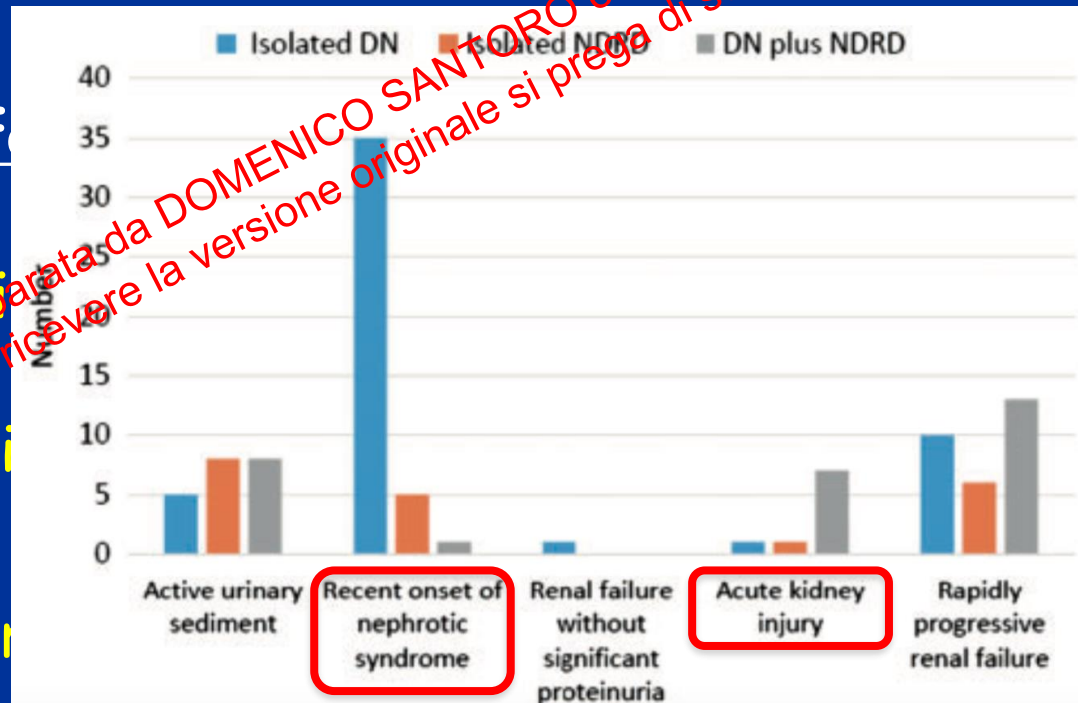
Clinical and pathological characteristics of non-diabetic renal disease in type 2 diabetes patients

Kittrawee Kritmetapak¹, Sirirat Anutrakulchai¹, Chatlert Pongchaiyakul² and Anucha Puapairoj³

Retrospective analysis of medical records of 101 T2DM pts who underwent renal biopsy under suspicion of NDRD from January 2011 through November 2015.

Indication for

- Nephrotic
- Progressive
- Active Urinary



ORIGINAL ARTICLE

Clinical and pathological characteristics of non-diabetic renal disease in type 2 diabetes patients

Kittrawee Kritmetapak¹, Sirirat Anutrakulchai¹, Chatlert Pongchaiyakul² and Anucha Puapairoj³

Multivariate analysis of clinical parameters in patients with NDRD with or without DN

Histology	NDRD superimposed on DN (N = 29)	Isolated NDRD (N = 20)	P-value
Acute tubular necrosis	14 (38.9)	0 (0)	<0.001
Acute interstitial nephritis	12 (33.3)	1 (5.0)	0.007
<u>IgA nephropathy</u>	1 (2.8)	7 (35.0)	0.005
<u>Membranous nephropathy</u>	0 (0)	5 (25.0)	0.008
Lupus nephritis	2 (5.6)	1 (20.0)	0.21
Crescentic glomerulonephritis	3 (8.2)	1 (5.0)	0.64
Membranoproliferative glomerulonephritis	0 (0)	1 (5.0)	0.22
Focal segmental glomerulosclerosis	1 (2.8)	0 (0)	0.41
IgM nephropathy	2 (5.6)	1 (5.0)	1.00
Chronic interstitial nephritis	1 (2.8)	0 (0)	1.00

Variables	OR	95% CI	P-value
Male gender	4.43	1.39–14.15	0.01
Duration of diabetes (>8 years)	0.15	0.04–0.49	0.002
Glycated hemoglobin (HbA1c)	0.16	0.05–0.47	0.001
Active urinary sediment ^a	4.75	1.46–15.43	0.01

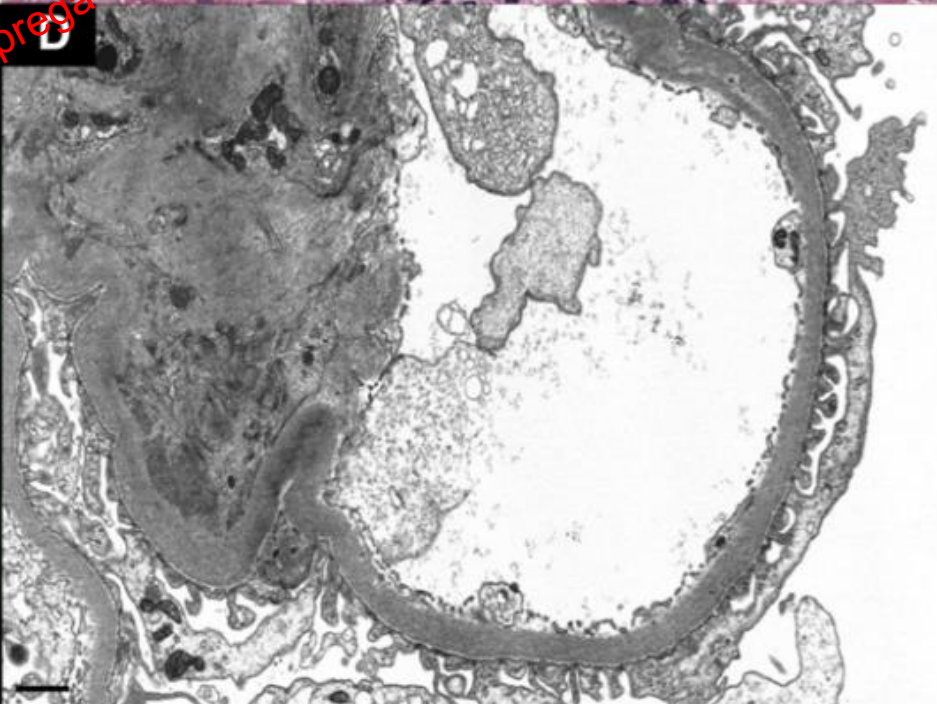
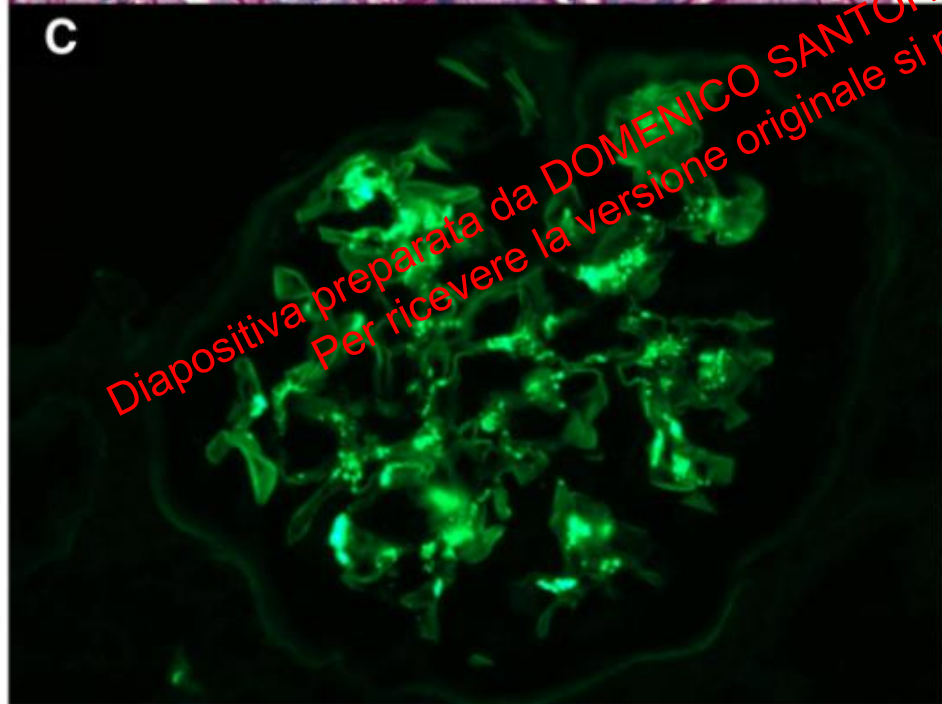
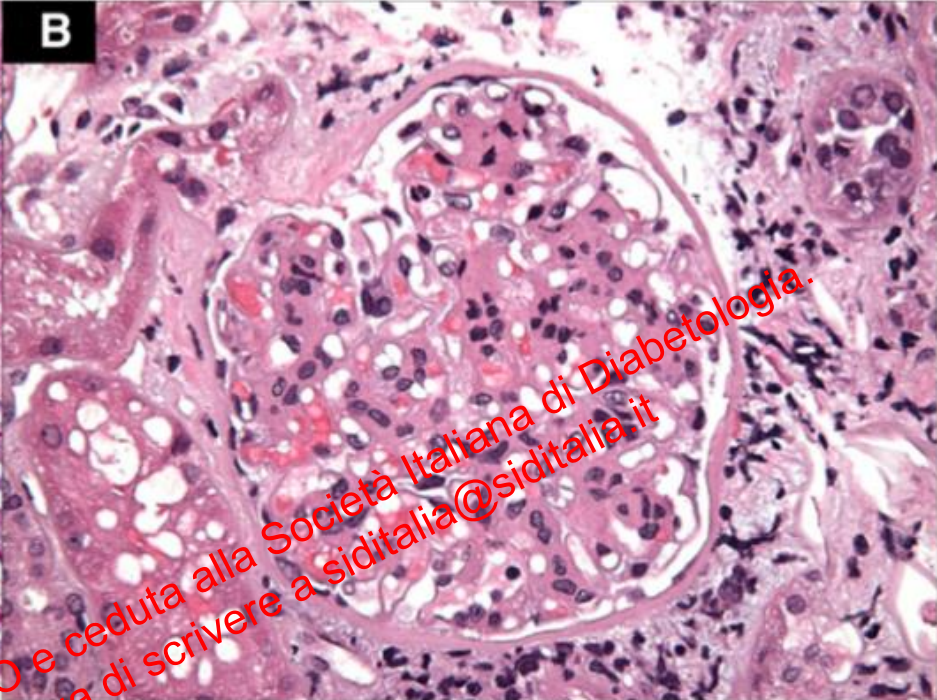
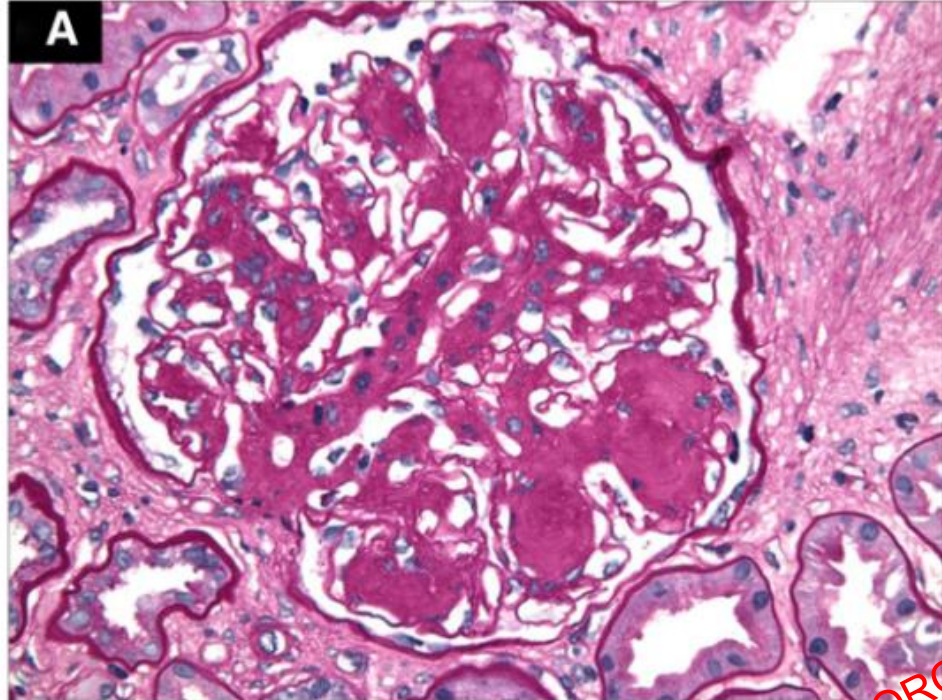
^aActive urinary sediment is defined as 10 or more red and white blood cells per high-power field.

The Modern Spectrum of Renal Biopsy Findings in Patients with Diabetes

Shree G. Sharma,* Andrew S. Bomback,* Jai Radhakrishnan,* Leal C. Herlitz,* Michael B. Stokes,* Glen S. Markowitz,* and Vivette D. D'Agati*

Consecutive native renal biopsies accessioned in the Columbia Renal Pathology Laboratory from **January through December 2011** were reviewed retrospectively for **clinical evidence of DM**.
Of **2642 native biopsies**, 620 diabetic patients (**23.5%**) were identified

Characteristics	DN Alone	DN Plus NDRD	NDRD Alone
Participants (n)	(37%) 227	(26%) 164	(36%) 220
Age (yr)	59 (49–68)	63 (55–72) ^a	63 (54–70) ^b
Male sex	129 (56.8)	100 (61.0)	142 (64.6)
Race			
Unknown	18 (47.6)	57 (34.8) ^a	104 (47.3) ^c
White	62 (27.3)	63 (38.4) ^a	70 (31.8)
African American	39 (17.2)	33 (20.1)	29 (13.2)
Hispanic	12 (5.3)	7 (4.3)	8 (3.6)
Asian	4 (1.8)	4 (2.4)	7 (3.2)
Other	2 (0.9)	0 (0.0)	2 (0.9)
DM type I	9 (4.0)	5 (3.1)	2 (0.9) ^b
Duration of DM (yr)	13 (8–17)	10 (7–18)	5 (3–10) ^{b,c}
Serum creatinine (mg/dl)	2.3 (1.6–3.8)	3.1 (1.7–5.2) ^a	2.3 (1.5–4.4) ^c
eGFR (ml/min per 1.73 m ²)	31.3 (17.5–55.2)	21.4 (12.5–46.6) ^a	32.5 (14.3–60.0) ^c
Proteinuria (g/d)	5.0 (2.8–8.8)	5.0 (2.0–8.0)	2.9 (1.4–7.1) ^{b,c}



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The Modern Spectrum of Renal Biopsy Findings in Patients with Diabetes

Shree G. Sharma,* Andrew S. Bomback,* Jai Radhakrishnan,* Leal C. Herlitz,* Michael B. Stokes,* Glen S. Markowitz,* and Vivette D. D'Agati*

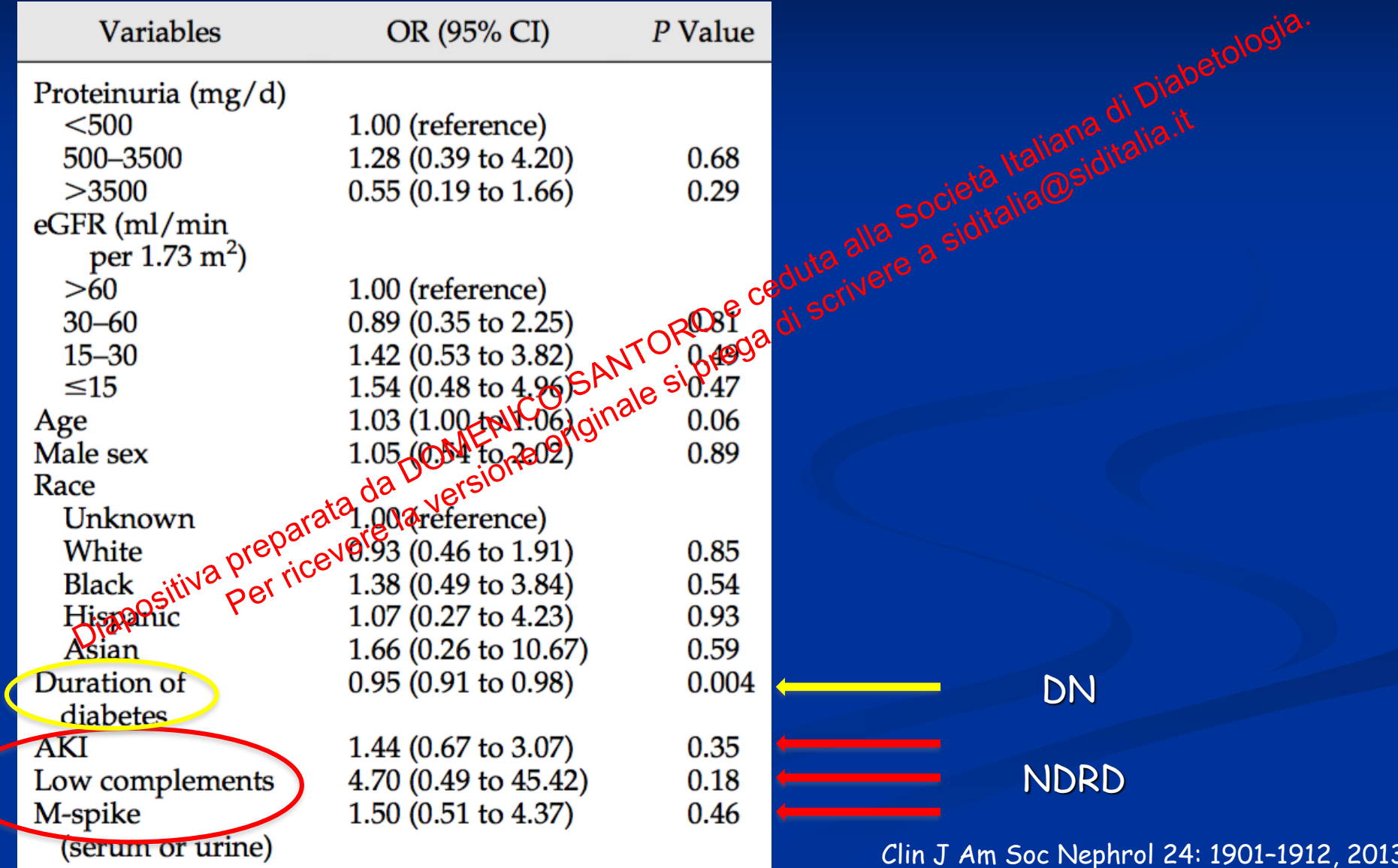


Types of NDRD (n)	NDRD Alone (n=220)	DN Plus NDRD (n=164)	P Value ^a
Acute tubular necrosis (109)	38 (17.3)	71 (43.3)	<0.001
FSGS (69)	48 (21.8)	21 (12.8)	0.02
Primary FSGS (6)	6 (2.7)	0 (0.0)	0.03
Secondary FSGS (63) ^b			
HTN related	19 (8.6)	10 (6.1)	0.35
HTN plus obesity related	16 (7.3)	10 (6.1)	0.65
Obesity related	4 (1.8)	1 (0.6)	0.30
Other ^c	3 (1.4)	0 (0.0)	0.13
Hypertensive nephrosclerosis (70) ^b	39 (17.7)	31 (18.9)	0.77
IgA nephropathy (35)	23 (10.5)	12 (7.3)	0.29
Membranous GN (23)	18 (8.2)	5 (3.0)	0.04
Pauci-immune crescentic GN (19)	15 (6.8)	4 (2.4)	0.05
Acute interstitial nephritis (18)	11 (5.0)	7 (4.3)	0.73
Amyloidosis (10)	10 (4.5)	0 (0)	0.01
Myeloma cast nephropathy (10)	8 (3.6)	2 (1.2)	0.14
Acute postinfectious GN (6)	3 (1.4)	3 (1.8)	0.72
Atheroembolic disease (5)	2 (0.9)	3 (1.8)	0.43
Others (10)	5 (2.3)	5 (3.0)	0.64

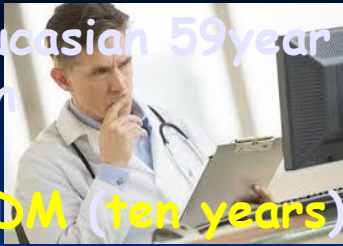
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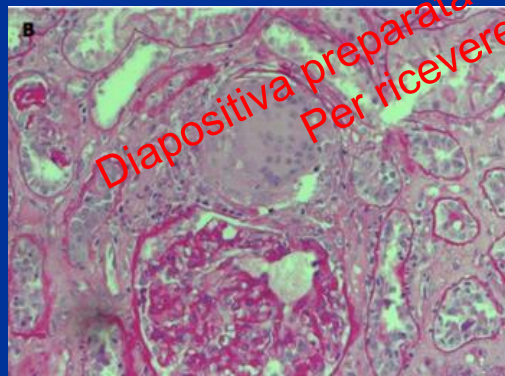
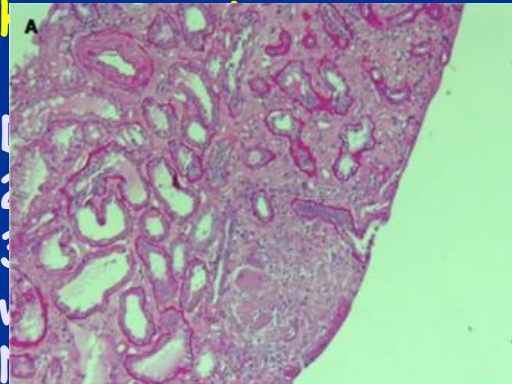
Variables	OR (95% CI)	P Value
Proteinuria (mg/d)		
<500	1.00 (reference)	
500–3500	1.28 (0.39 to 4.20)	0.68
>3500	0.55 (0.19 to 1.66)	0.29
eGFR (ml/min per 1.73 m ²)		
>60	1.00 (reference)	
30–60	0.89 (0.35 to 2.25)	0.81
15–30	1.42 (0.53 to 3.82)	0.46
≤15	1.54 (0.48 to 4.96)	0.47
Age	1.03 (1.00 to 1.06)	0.06
Male sex	1.05 (0.54 to 2.02)	0.89
Race		
Unknown	1.00 (reference)	
White	0.93 (0.46 to 1.91)	0.85
Black	1.38 (0.49 to 3.84)	0.54
Hispanic	1.07 (0.27 to 4.23)	0.93
Asian	1.66 (0.26 to 10.67)	0.59
Duration of diabetes	0.95 (0.91 to 0.98)	0.004
AKI	1.44 (0.67 to 3.07)	0.35
Low complements	4.70 (0.49 to 45.42)	0.18
M-spike (serum or urine)	1.50 (0.51 to 4.37)	0.46



Caucasian 59 year old man



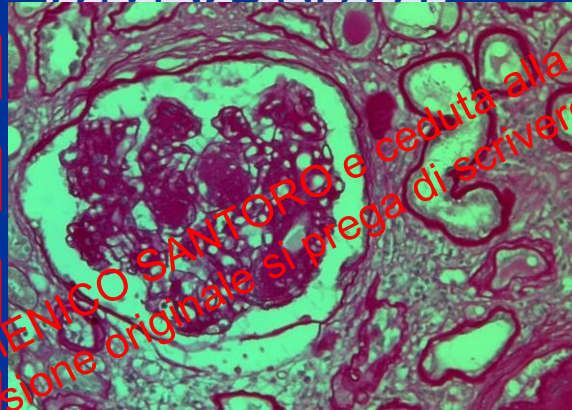
T2DM (ten years), with poor glycaemic control ($HbA1c = 10.1\%$) and Renal Sarcoidosis



Caucasian 59 year old woman



T2DM ($HbA1c = 6.4\%$) with hypertension; diabetic Nephropathy retinopathy, cerebral ischemic episodes



Admission to the Nephrology Unit

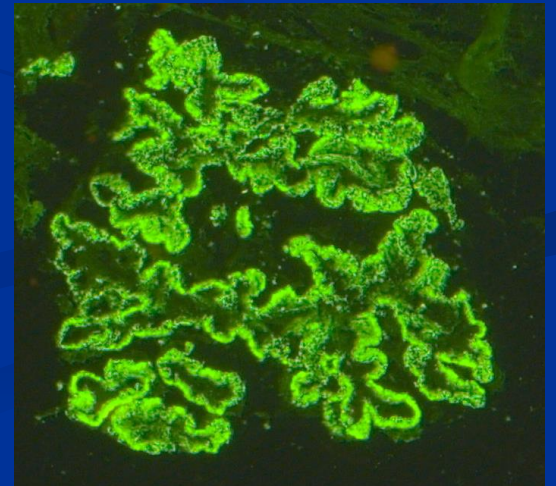
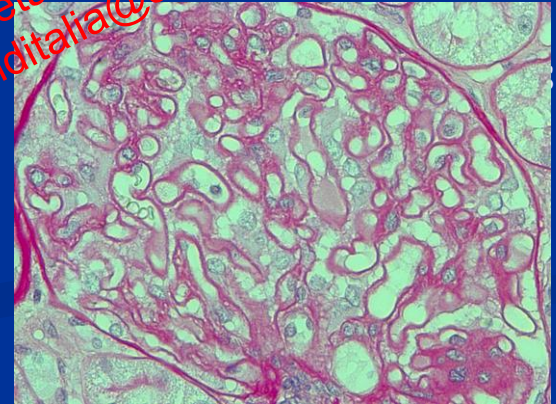
Screening for autoimmunity, complement level IFS and IFU and hepatitis were all negative



Caucasian 59 year old man

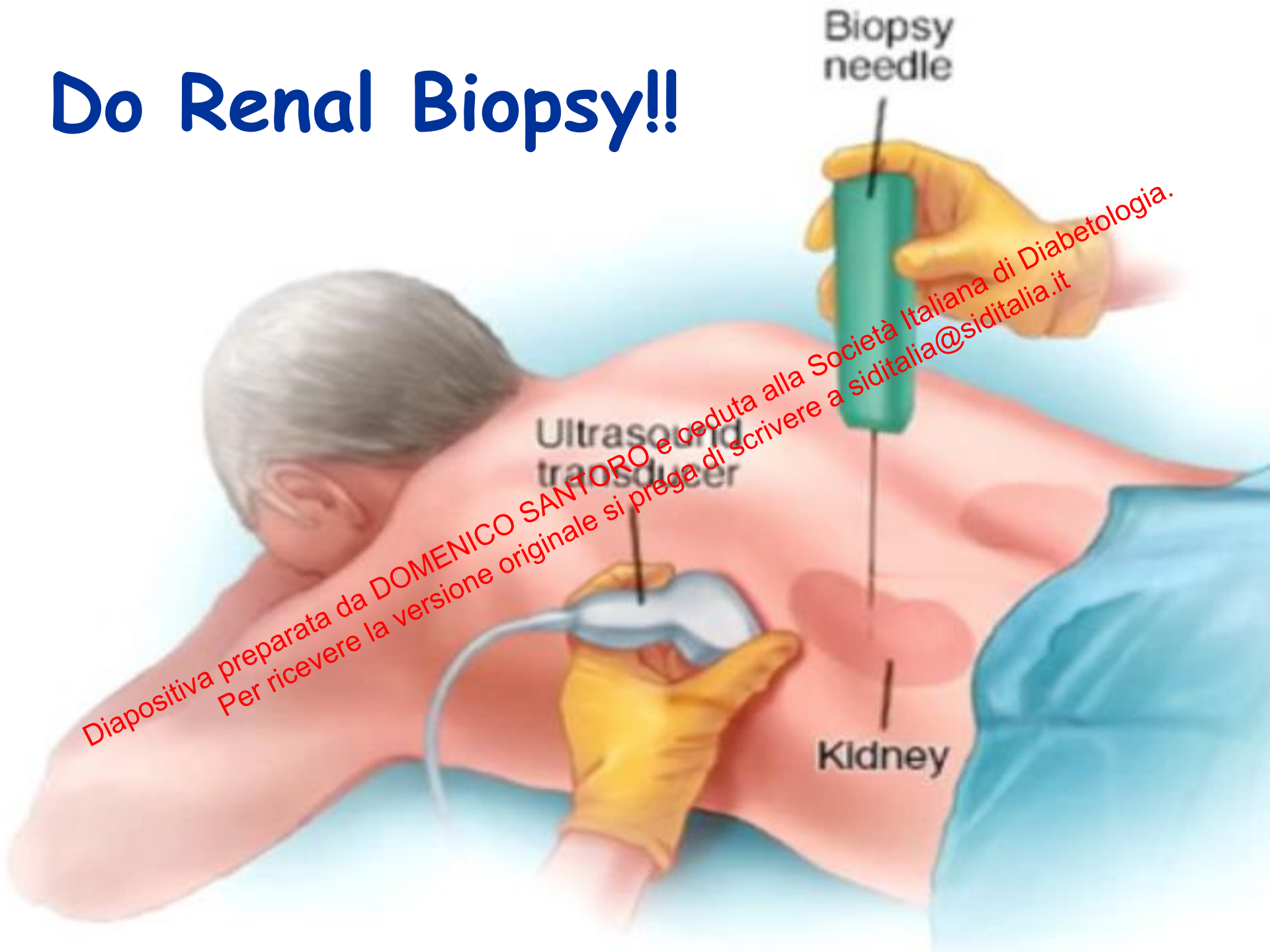


T2DM ($HbA1c = 7.4\%$), ischaemic Nephropathy, hypertension



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Do Renal Biopsy!!



Home take messages

About 1/3-1/4 of diabetic patients will present Diabetic Nephropathy

DN is the leading cause of ESRD in western countries.

Recent data show that renal biopsy in diabetic patients is increasing (25% cases of Columbia) and in 2/3 of cases a renal damage non-DM correlated can be found.

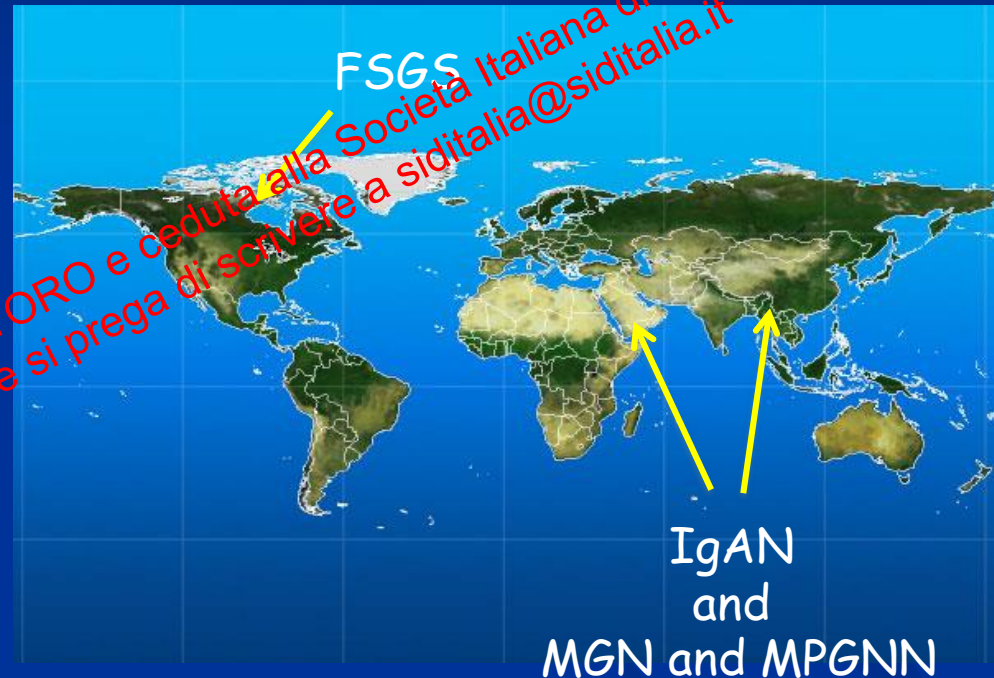
Clinical, labs and instrumental parameters may help nephrologist to guide in decision of RB:

- Duration of DM
- Diabetic Retinopathy
- Glomerular Hematuria
- Other renal or systemic alterations

Home take messages

There are different type of **NDRD** (**MN**, **IgAN**, **FSGS** etc) that may occur in DM and most of them can receive a **specific treatment**.

Incidence and prevalence may vary in relation of **indication of RB** and **geographic areas**.



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Grazie per l'attenzione!