X CONGRESO AADEA

Málaga del 14 al 15 febrero 2020

Sd. Sjogren y Riñón

Martín-Gómez A. ***Nefrología.*** *Hospital de Poniente.* ***El Ejido***

Tabla 1 – Ítems que evalúan las herramientas clinimétricas en SSp y cómo se puntúan

	SSDDI	SSDAI	SSDI	PROFAD - SSI - SF	ESSDAI	ESSPRI
DOMINIOS EVALUADOS	Enfermedad linfoproliferativa	Síntomas constitucionales	Dominio ocular	Necesidad de descansar	Dominio constitucional	Sequedad
	Daño renal	Síntomas articulares	Dominio oral	Dificultad para iniciar una actividad	Dominio de linfadenopatía y linfoma	Fatiga
	Daño ocular	Características hematológicas	Dominio sistémico	Dificultad para continuar con una actividad	Dominio glandular	Dolor
	Daño Oral/Salivar	Síntomas pleuro-pulmonares		Dificultades por sentir falta de fuerza en los	Dominio articular	
					Dominio cutáneo	
					Dominio	
					Dominio renal	
					Dominio muscular	
					Dominio de sistema nervioso periférico	
					Dominio de sistema nervioso central	
					Dominio hematológ	
					Dom	
					para humedece	oca
					Molestias por otros problemas	

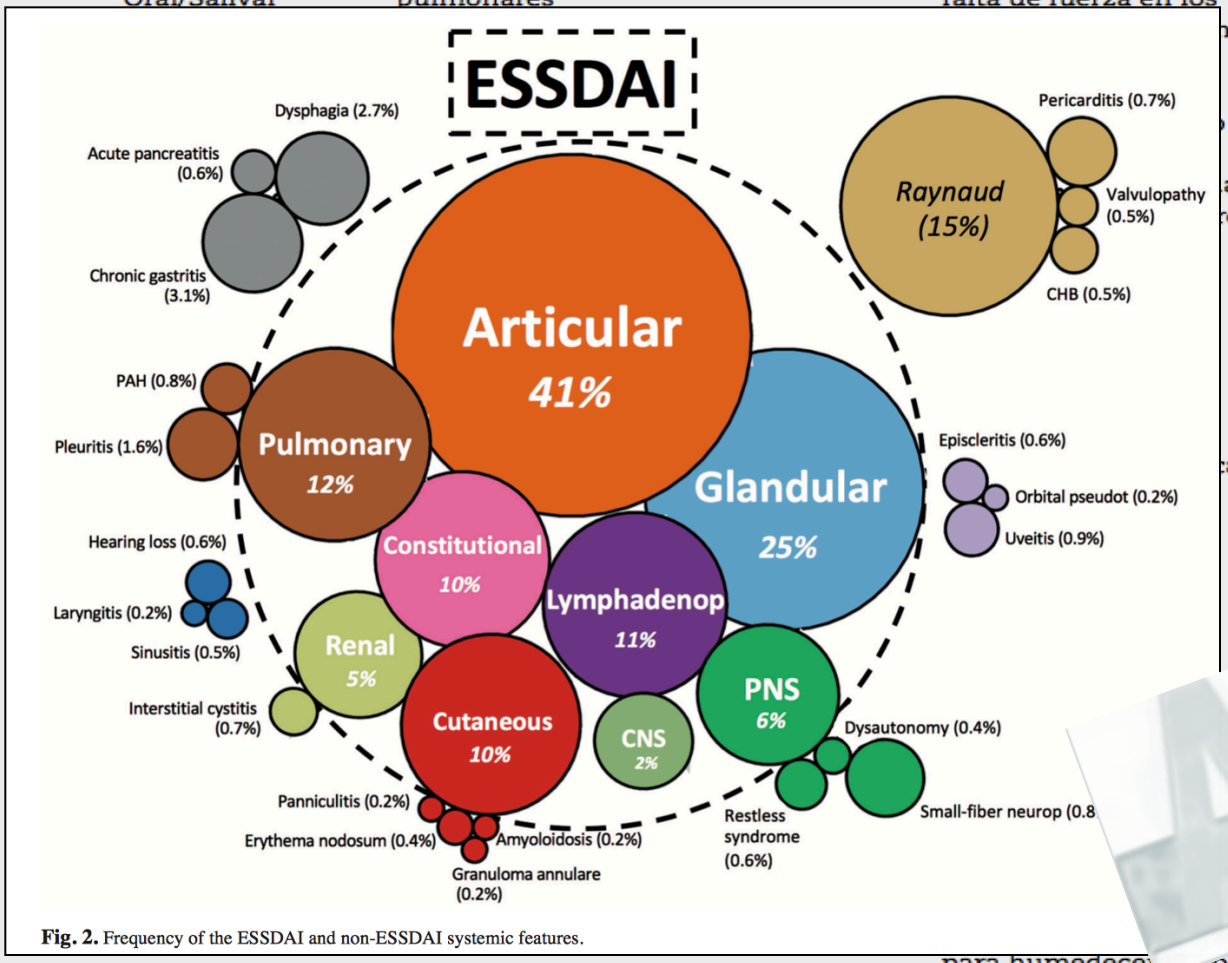
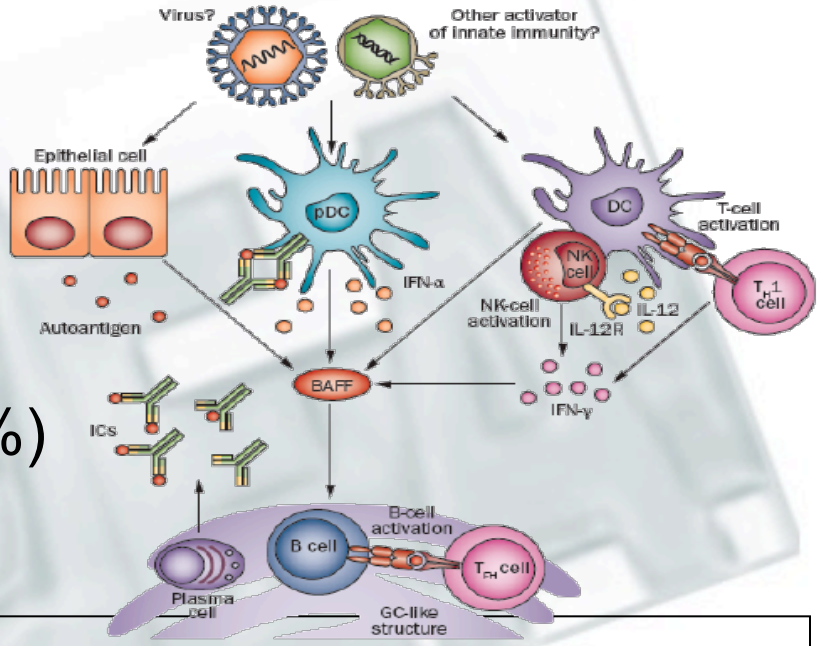


Fig. 2. Frequency of the ESSDAI and non-ESSDAI systemic features.

Sd.Sjogren. Clínica **Extra-Glandular**

- ANA (85%)
- AntiRo (40-80%)
- AntiLa (40%)
- FR (50%)
- Crioglobulinas (IgM) (13%)
- Hipergammaglobulinemia (22%)
- C3 bajo (8%), C4 bajo (18%)



- Astenia 70%
- Sd.Constitucional 10-15%
- Artralgias 48%, Artritis 15%
- Fenóm. Raynaud 18%
- Pulmón 11%
- SNP 11%
- Cutáneo 10%
- Vasculitis (cutánea) 9%
- **Renal 5%**
- SNC 2%

Sd.Sjogren y Riñón (2-67%: **30%**)

- La incidencia y prevalencia de afectación renal en el SSp **NO está establecida** en la literatura:

- Diferencias geográficas y **étnicas**…(Asia)
- Mayoría de los estudios: **retrospectivos**
- Algunas series incluyen **SSp** y **SSs**.
- Diferentes **criterios** diagnósticos/clasificación del SS.
- Diferentes **definiciones** de afectación renal (hallazgos de laboratorio, histopatológicos, clínicos…)
- **Latente/Subclínica** (30%) vs **Florida/Clínica** (1-9%).
- Nefritis **TubuloIntersticial** >>>>> Glomerulonefritis

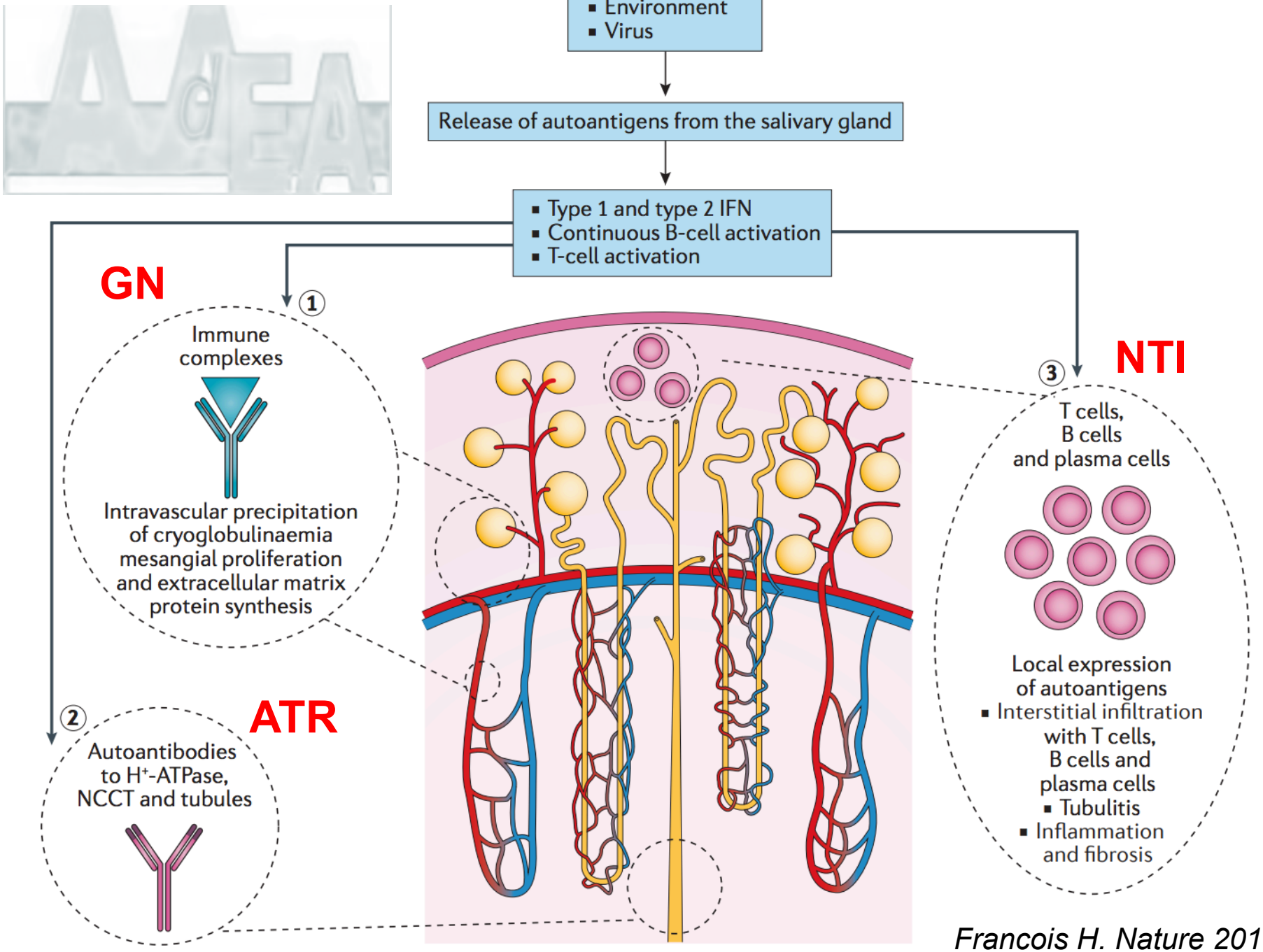
Sd.Sjogren y Riñón (2-67%: **30**%)

Table 1 | **Prevalence of renal involvement in patients with primary Sjögren syndrome**

Study	Country	Diagnostic criteria	Number of patients	Renal involvement % (*n*)
Goules *et al.* (2000)[28]	Greece	European–1993*	471	4.2 (20)
Skopouli *et al.* (2000)[71]	Greece	At least 3 AECG criteria	261	11.0 (30)
Bossini *et al.* (2001)[3]	Italy	European–1993*	60	27.0 (16)
Garcia-Carrasco *et al.* (2002)[72]	Spain	European–1993*	400	6.0 (25)
Ramos-Casals *et al.* (2008)[73]	Spain	AECG or European–	1010	5.0 (48)
Maripuri *et al.* (2009)[21]	USA	AECG	7,276	0.3 (24)
Lin *et al.* (2010)[8]	China		473	33.5 (192)
Seror *et al.* (2010)[13]	Europe		96	14.58 (14)
Malladi *et al.* (2012)[6]	International		886	1.0 (9)
Goules *et al.* (2013)[25]	Greece		715	4.9 (35‡)
Gottenberg *et al.* (2013)[14]	France		395	2.8 (11)
Ramos-Casals *et al.* (2014)[74]	Spain	AECG	921	4.3 (40)
Baldini *et al.* (2014)[7]	Italy	AECG and/or European–1993*	1115	1.7 (19)

La prevalencia de la afectación renal se establece entre un 5-9 % aunque hay series grandes en la que la prevalencia sube hasta un 33%

Francois H. Nature 2015



Francois H. Nature 2015

Sd.Sjogren y Riñón (2-67%: **30**%)

- La presentación clínica es muy heterogénea y pasa a menudo desapercibida:

  - Edad **>50 años***
  - Tiempo: **2-7 años** después del debut del SSp*.

  - **Tubulopatías**:
  - **ATRd**: hipercalciuria, nefrolitiasis, nefrocalcinosis.
  - Diabetes Insípida Nefrogénica
  - Sd.Fanconi
  - Sd.Bartter/Gitelman
  - **NTIA, NTIC**
  - **GN: GNMP** (Crioglobulinemia), NIgA, GNMB…

Chin Med J 2010;

Clinical and prognostic characteristics of 573 cases of primary Sjögren's syndrome

LIN Dong-fang

N=192/573 (33.5%) afectación renal:

- **Proteinuria** 126 (22%) (0.5 ± 0.1g/d)
- **ATR** 96 (17%), st ATRd/tipo I (88, 92%).
  - Nefrolitiasis/Nefrocalcinosis 45/481 (9.4%).
- **Insuficiencia renal** 41 (7.2%).

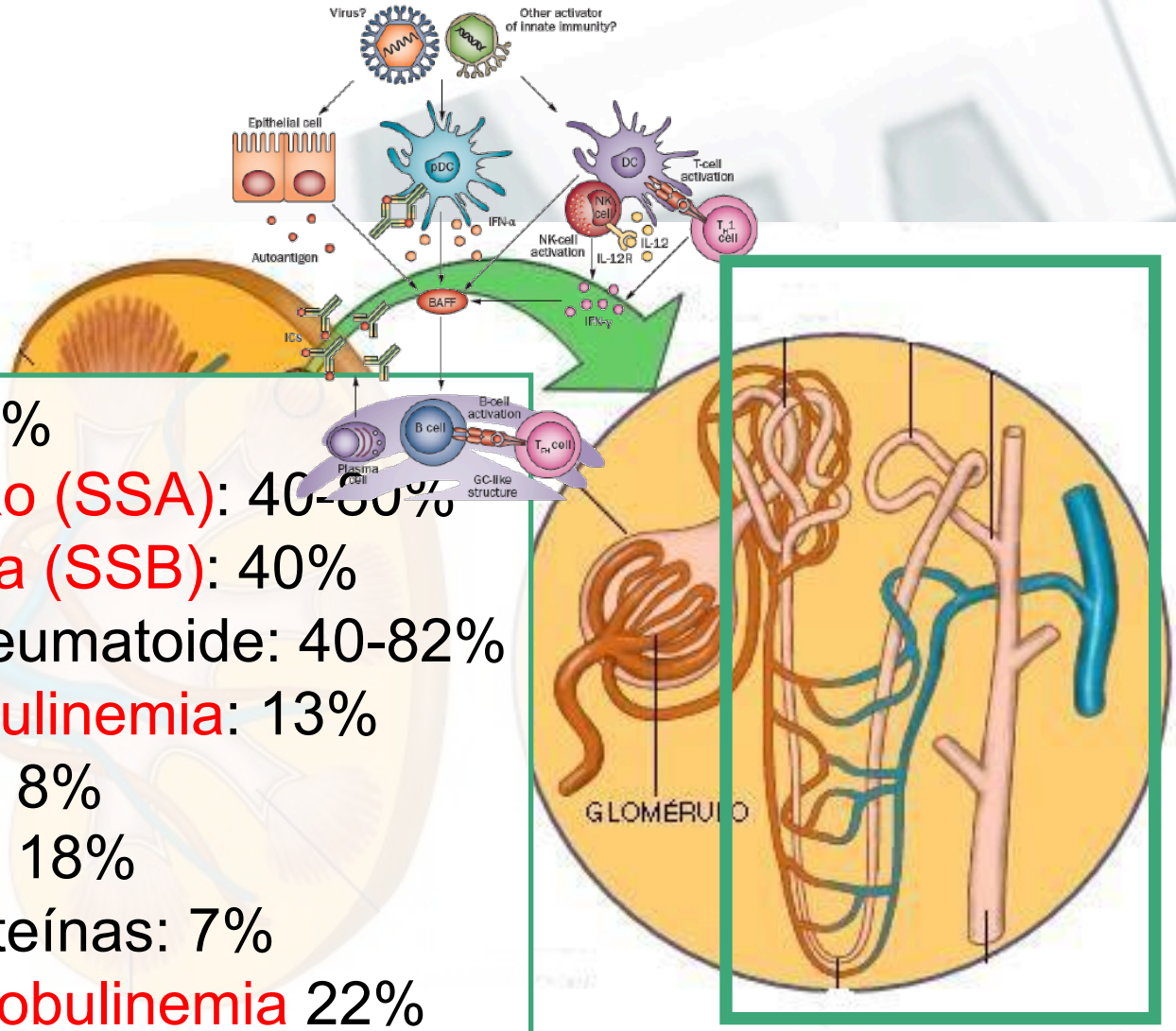
Biopsia renal 64: 21 **NTI**,24 **GN**,16 NTI+GN,1 NTA

12 GN **MSG**
10 GN **MB**
9 GN**MP**
4 GN **proliferativa focal**
4 GN **proliferativa difusa**
1 **Enf. MB Adelgazada**.

Table 2. Comparisons of system involvement in pSS patients in different studies

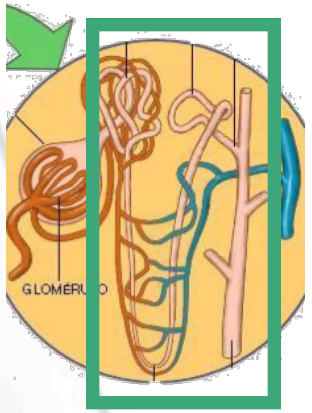
Variables	This study	Zhao et al[3]	García-Carrasco et al[4]	Skopouli et al[5]	Davidson et al[6]	Alamanos et al[7]	Ramos-Casals et al[8]	Theander et al[9]
n	573	116	400	261	74	442	336	286
Fever (% (*n*))	41.0 (235)	15.6 (18)	6.0 (24)*	16.9 (44)*	–	–	–	–
Fatigue (% (*n*))	27.7 (159)	–	–	36.4 (95)¶	86.5 (64)*	–	–	–
Swelling of lymph nodes (% (*n*))	7.7 (44)	19.8 (23)	7.0 (28)	31.8 (83)*	18.9 (14)†	6.6 (28)	6.8 (23)	–
Purpura (% (*n*))	13.4 (77)	25.0 (29)‡	–	11.1 (29)	–	4.7 (20)	–	11.9 (29/244)
Raynaud's phenomenon (% (*n*))	17.6 (101)	12.9 (15)	15.5 (62)	47.5 (124)*	62.2 (46)*	34.6 (146)	–	–
Articular (% (*n*))	47.8 (274)	46.6 (54)	36.8 (147)†	74.7 (195)*	85.1 (63)*	39.0 (165)	42.0 (120)	–
Myositis (% (*n*))	4.9 (28)	3.4 (4)	1.3 (5)‡	1.1 (3)‖	–	–	–	–
Hematological (% (*n*))	49.6 (284)	–	–	–	–	–	–	–
Pulmonary (% (*n*))	42.3 (221/522)	10.3 (12)*	9.3 (37)*	29.9 (78)†	–	2.6 (11)*	9.5 (32)*	–
Cardiac effusion (% (*n*))	14.8 (52/352)	1.7 (2)*	–	1.5 (4)*	–	–	–	–
Hepatic (% (*n*))	32.8 (188)	17.2 (20)†	–	–	–	–	–	–
Pancreatic (% (*n*))	5.6 (27/481)	2.6 (3)	1.0 (4)*	–	–	–	–	–
Renal (% (*n*))	33.5 (192)	36.2 (42)	6.3 (25)*	11.5 (30)*	–	–	–	–
Thyroid (% (*n*))	32.7 (74/226)	–	15.3 (61)*	–	16.2 (12)*	–	–	–
Neurologic (% (*n*))	11.9 (68)	12.1 (14)	8.3 (33)	2.3 (6)*	5.4 (4)	–	7.1 (24)	–

Sd.Sjogren y Riñón (2-67%: **30**%)



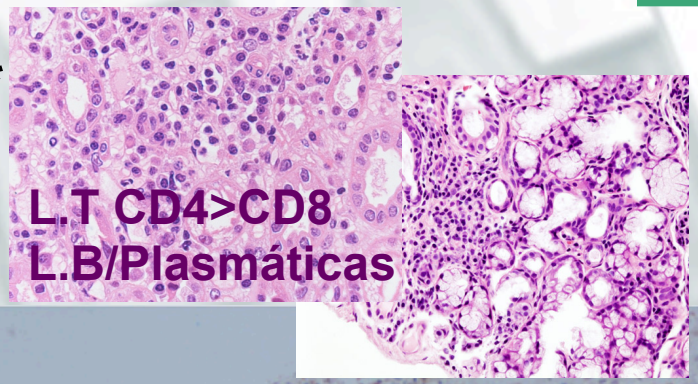
- ANA: 85%
- Ac AntiRo (SSA): 40-80%
- Ac AntiLa (SSB): 40%
- Factor reumatoide: 40-82%
- Crioglobulinemia: 13%
- C3 bajo: 8%
- C4 bajo: 18%
- Paraproteínas: 7%
- Hiperγglobulinemia 22%
- CLL, antiATPasa, antiAC…

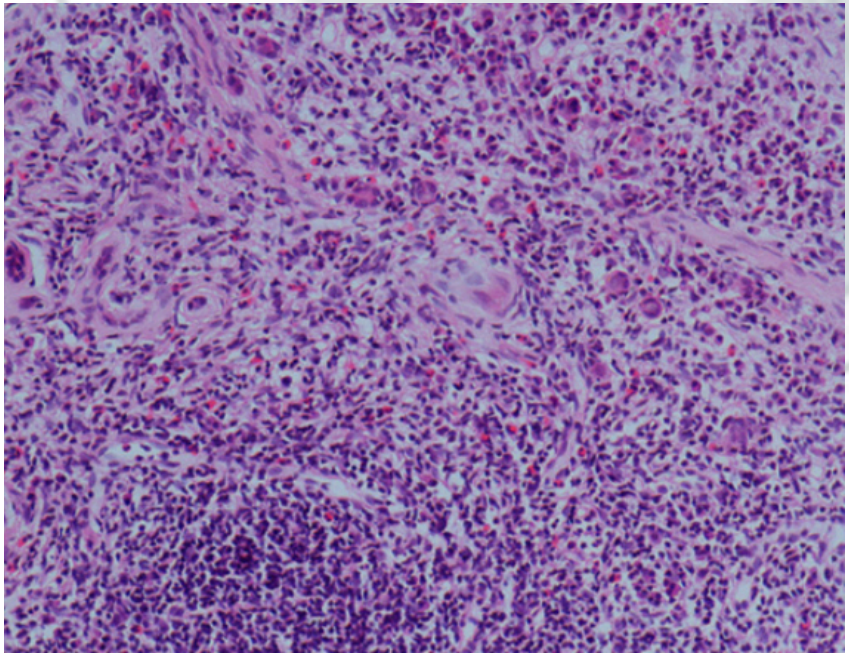
Daño **tubular** SSp **30%**

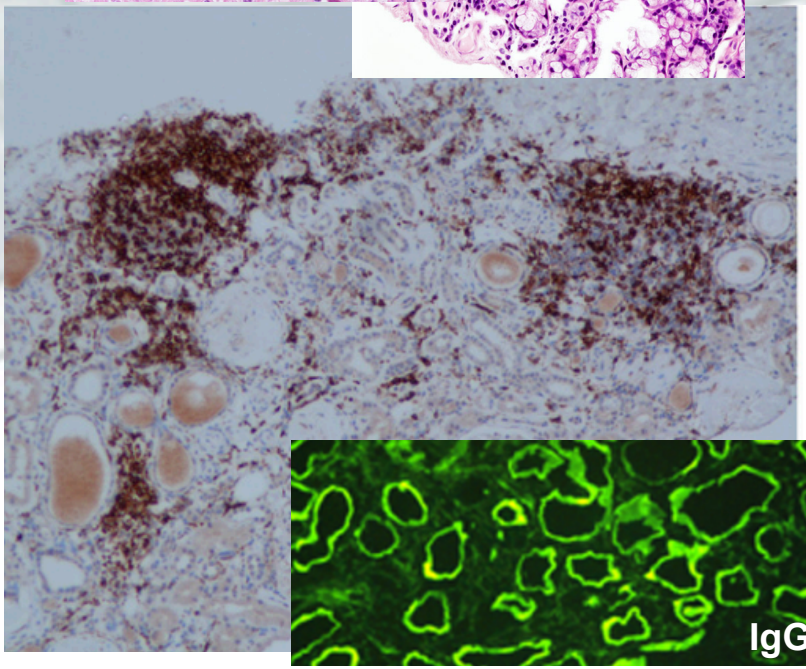


- Etiología: viscosidad de Hiperγglobulinemia, CLL, **infiltración** peritubular linfocitaria/plasmáticas.

- AP: **Nefritis Tubulointersticial***
  NTA







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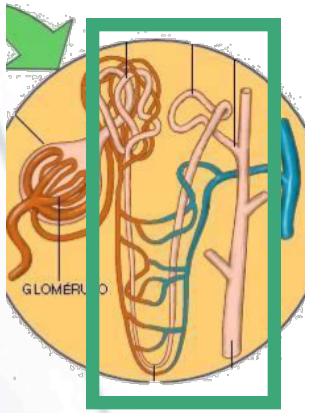

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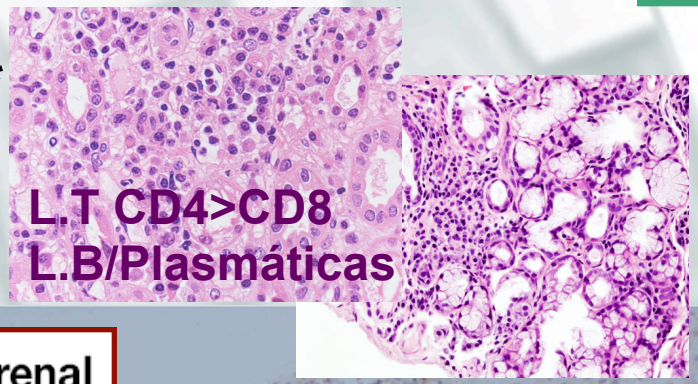
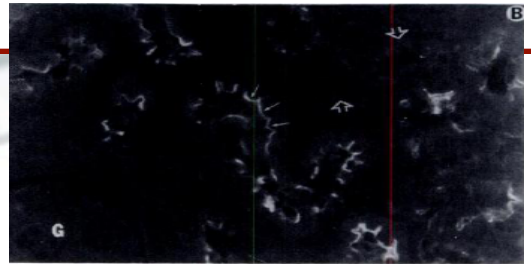
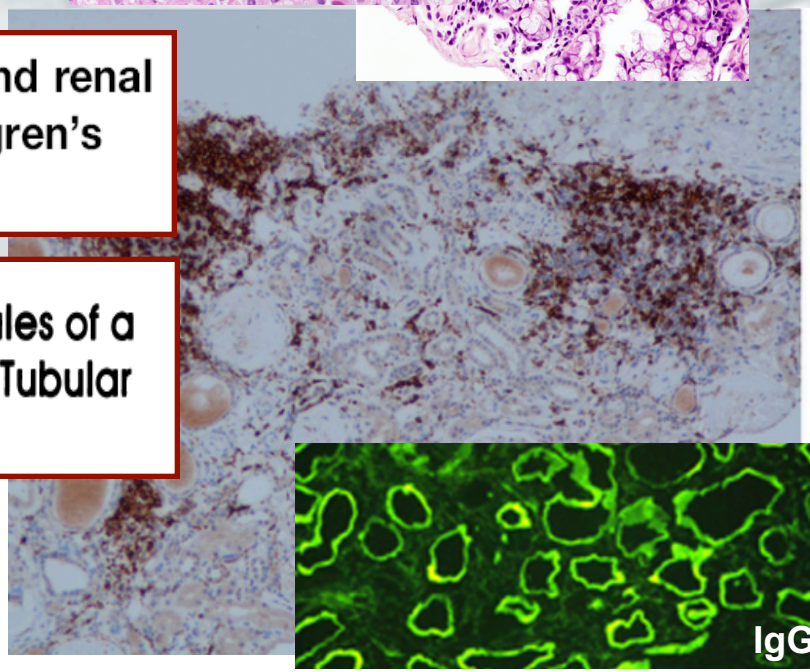


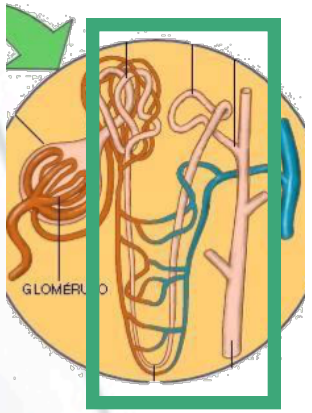
Novel carbonic anhydrase autoantibodies and renal manifestations in patients with primary Sjögren's syndrome

Absence of H^+-ATPase in Cortical Collecting Tubules of a Patient with Sjogren's Syndrome and Distal Renal Tubular Acidosis[1,2]





Daño **tubular** SSp **30%**



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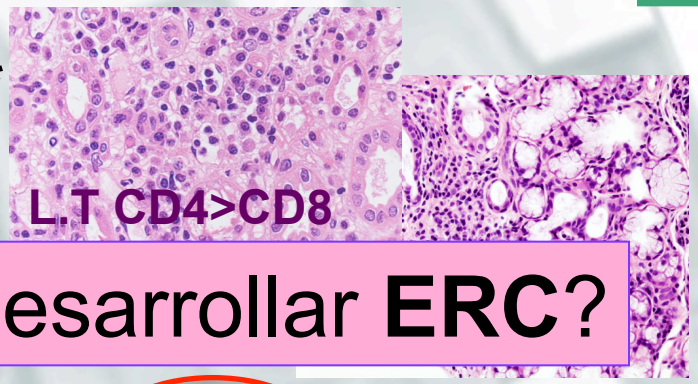
- AP: **Nefritis Tubulointersticial***
  NTA

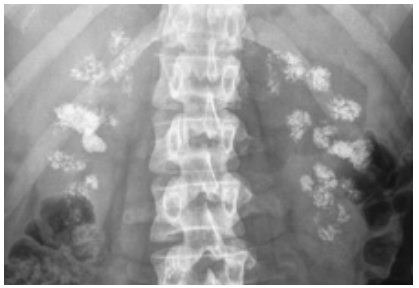


- Clínica: I

¿Posibilidad de desarrollar **ERC**?

- **Acidosis Tubular distal**>proximal: pHo↑, ↓K (calambres, paresias, arritmia), ↓ P (hemólisis), ↓ Vit.D (osteomalacia) hipercalciuria, glucosuria (poliuria)…

  → **Litiasis/nefrocalcinosis**: CRU, IRA.



- **AUA** (hematuria, proteinuria TUBULAR)

- **Sd.Nefrítico**: IRA, hematuria, proteinuria, HTA.

Scand J Rheumatol Suppl 1986

Glomerular filtration rate in primary Sjögren´s syndrome with renal disease.

Eriksson P

- **N= 27**

- **ATRd 18/27 (77%) → 8/18 (44%) ↓ GFR.**

- **↓ GFR (**51 Cr-EDTA) **9/27 (33%):**
  - **ATRd 8/9**
  - **Urolitiasis 6/9**
  - **ITU 2/9**
  - **NTI 5/6 bx.**

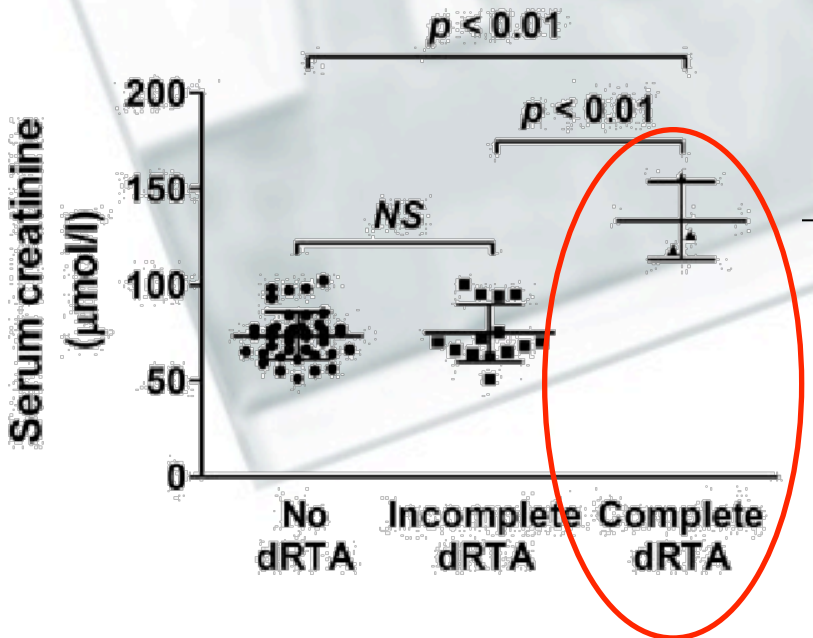
RHEUMATOLOGY
2015

Prevalence of distal renal tubular acidosis in primary Sjögren's syndrome

Tim Both

N=57 SSp asintomáticos → 17/57 (30%) ATRd

	ATRd completa n= 3/17 (5%)	ATRd incompleta n=14/17 (25%)	No ATRd n=40 (70%)	
SSB/La+	**100%**	**79%**	**45%**	P<0.05
ESSDAI	3 (1.9)		2.4 (1.9)	DNS
Duración (a)	13 (5)		11.4 (8)	



→ eGFR < 60 ml/min/1.73m^2

J Intern Med. 1996

Urolithiasis and distal renal tubular acidosis preceding primary Sjögren's syndrome: a retrospective study 5-53 years after the presentation of urolithiasis.

Eriksson P

- 10 pacientes con **UROLITIASIS** y **ATRd** pero no sintomatología de SS:

- 8/10 **antiRo +**
- 4/5 **NTI** (bx).
- Al cabo de 15 años (1-48) → 7/8 pacientes con antiRo desarrollaron SS

La nefropatía puede preceder al Sd.Seco

Pedir **antiRo/La** en las UROLITIASIS con ATR

J Clin Rheumatol 2010;

Hypokalemic Paralysis as Primary Presentation of Fanconi Syndrome Associated With Sjögren Syndrome

Chih-Chiang Wang

N= 12 casos en la literatura de **Fanconi** en SSp

TABLE 2. A Summary of SS-Related FS

Reference	Sex/Age	Presenting Symptoms	dRTA	Urine pH	CD	Cr	CCr	K^+	Histology	Treatment	Outcome
Shearn and Tu[7]	F/34	Polyuria*	+	>6.2	+	n.a.	37	3.8	TIN, tubular atrophy	n.a.	n.a.
Walker et al[8]	F/28	Paralysis, polyuria*	+	6.8	+	n.a.	n.a.	n.a.	TIN	Prednisolone 10 mg/d	n.a.
Kamm and Fischer[9]	F/60	Polyuria, nocturia, weight loss*	+	6.2	+	2.7	19	2.9	Diffuse TIN	Supportive only†	Improved‡§
Matsumura et al[10]	F/35	n.a.	n.a.	n.a.	n.a.	2.7	23	n.a.	TIN, Tubulitis	n.a.	n.a.
Ardiles et al[11¶]	F/52	Muscle weakness‖	+	7.0	n.a.	1.3	n.a.	2.5	n.a.	Prednisolone "low dose"	Improved§
Bridoux et al[12]	M/69	Weight loss‖	+	>6	+	1.8	33	3.5	Diffuse TIN, Proximal tubulitis	Supportive only†	Die**
Bridoux et al[12]	F/33	Polyuria††	+	>6.5	+	1.6	50	2.4	Diffuse TIN, Proximal tubulitis	Prednisolone 10 mg/d	Improved‡§
Kobayashi et al[13]	F/49	Muscle weakness††	+	7.5	+	1.3	33	2.7	Diffuse TIN, proximal tubules atrophy	Prednisolone 30 mg/d, 6 mo later 12.5 mg/d	Improved‡§
Yang et al[14]	F/60	Muscle weakness, respiratory distress‖	+	8.5	n.a.	1.4	n.a.	2.7	n.a.	Supportive only†	n.a.
Our case	M/39	Hypokalemic paralysis‖	+	7.0	+	2.2	48	1.6	Diffuse TIN	Mycophenolate mofetil 1 g/d	Improved‡§

Q J Med 2000; 93:297–304

Renal involvement in primary Sjögren's syndrome

K. AASARØD, H.-J. HAGA[1], K.J. BERG[2], J.

Table 2 Overview of markers of renal disease in 62 patients with primary Sjögren's syndrome

Variable	Fraction abnormal	Reference values
Creatinine clearance/1.73 m^2	21.0% (13/62)	Age-adjusted
Urine concentration capacity	21.0% (13/62)	Age-adjusted
Citrate in 24-h urine	25.8% (16/62)	3.09 (1.24–5.67) mmol
Citrate in spot urine	19.4% (12/62)	0.22 (0.10–0.50) mmol/mmol creatinine
β_2-microglobulin in 24-h urine	45.2% (28/62)	3.36–21.92 µg/mmol creatinine
NAG in 24-h urine	41.9% (26/62)	0.02–0.27 U/mmol creatinine
ALP in 24-h urine	14.5% (9/62)	0.05–0.65 U/mmol creatinine
Kallikrein in 24-h urine	29.0% (18/62)	14–201 $U \times 10^{-2}$
Fractional sodium excretion	1.6% (1/62)	<2%
Glucosuria	1.6% (1/62)	0 arb. units
Albumin in 24-h urine	1.6% (1/62)	<30 µg/min
dRTA	11.3% (7/62)	

Patient	dRTA	Urine pH*	Base excess*	Max. urine osmolality** (mosmol/kg)	Creatinine clearance (ml/min/1.73m^2)	24-h urine albumin (µg/min)***
1	Complete	6.77	−4.8	761	61§	4.0
2	Complete	6.91	−8.0	332§	47§	6.8
3	Complete	6.35	−7.0	501§	87	0.0
4	Complete	5.71	−5.7	521§	37§	38.0
5	Incomplete	5.88	−5.7	809	65	4.6
6	Incomplete	5.83	−6.9	501§	76	0.0
7	Incomplete	5.78	−4.9	518§	43§	12.8

Rheumatology 1999

The occurrence of renal involvement in primary Sjögren's syndrome: a study of 78 patients

M. Pertovaara[1], M. Korpela[1], T. Kouri[2]

TABLE 1. Renal findings in 78 patients with primary Sjögren's syndrome

Variable		Frequency
Urinalysis		
Dipstick for albumin positive		3 (4%)
Dipstick for erythrocytes positive		13 (17%)
Dipstick for leucocytes positive		21 (27%)
Urine microscopy		
Erythrocytes > 1/HPF		4 (5%)
Leucocytes > 2/HPF		12 (15%)
Culture for urine bacteria positive		10 (13%)
Mild proteinuria (0.15–0.42 g/24 h)		34 (44%)
Urine light chains		1 (1%)
Increased urinary excretion rates of		
IgG (≥ 5.0 μg/min)		11 (14%)
Albumin (≥ 20 μg/min)		9 (12%)
α1-Microglobulin (≥ 7.0 μg/min)		9 (12%)
Lysozyme		1 (1%)
Kidney ultrasound abnormal		20 (26%)
Nephrography abnormal		26 (33%)
Ammonium chloride loading test abnormal or overt RTA	$n = 55$	18 (33%)

GFR **76.2 ± 26**

ml/min/1.73m^2.

(19%<60$_{ml/min/1.73m^2}$)

Rheumatology 1999

The occurrence of renal involvement in primary Sjögren's syndrome: a study of 78 patients

M. Pertovaara[1], M. Korpela[1], T. Kouri[2]

Variable	Urine acidification capacity: Inadequate ($n = 18$)	Normal ($n = 37$)	Significance
Age, mean (yr)	57 ± 13	57 ± 13	NS
Duration of sicca symptoms of the eyes (yr)	12 ± 6	11 ± 7	NS
Duration of xerostomia (yr)	15 ± 8	10 ± 6	$P \leqslant 0.025$
Duration of the disease (yr)	10 ± 4	8 ± 4	$P \leqslant 0.05$
Frequency of hypertension	8 (44%)	5 (14%)	$P \leqslant 0.05$
Serum creatinine (μmol/l)	92 ± 39	78 ± 13	$P \leqslant 0.025$
Creatinine clearance (ml/s/1.73 m^2)	1.22 ± 0.44	1.37 ± 0.37	NS
Frequency of proteinuria (⩾0.15 g/24 h)	12 (67%)	10 (27%)	$P \leqslant 0.02$
cU IgG (⩾5.0 μg/min)	2 (11%)	3 (8%)	NS
cU albumin (⩾20 μg/min)	2 (11%)	1 (3%)	NS
cU α1-microglobulin (⩾7.0 μg/min)	2 (11%)	2 (5%)	NS
ANA positive	17 (94%)	32 (87%)	NS
Anti SS-A antibodies positive	16 (89%)	26 (72%)	NS
Anti SS-B antibodies positive	13 (72%)	18 (50%)	NS
Serum IgG (g/l)	21.7 ± 7.3	19.7 ± 6.7	NS
Serum β2m (mg/l)	3.27 ± 1.60	2.60 ± 0.58	$P \leqslant 0.025$

Variable	Urinary total protein excretion (g/24 h): ⩾0.15 ($n = 34$)	<0.15 ($n = 44$)	Significance
Age, mean (yr)	59 ± 13	58 ± 13	NS
Duration of sicca symptoms of the eyes (yr)	11 ± 7	11 ± 7	NS
Duration of xerostomia (yr)	14 ± 9	11 ± 6	$P \leqslant 0.05$
Duration of the disease (yr)	10 ± 4	9 ± 5	NS
Frequency of hypertension	9 (27%)	9 (21%)	NS
Systolic blood pressure (mmHg)	143 ± 20	134 ± 16	$P \leqslant 0.025$
Diastolic blood pressure (mmHg)	86 ± 11	82 ± 9	$P \leqslant 0.025$
Serum creatinine (μmol/l)	88 ± 31	81 ± 19	NS
Creatinine clearance (ml/s/1.73 m^2)	1.21 ± 0.46	1.33 ± 0.41	NS
Abnormal urine acidification capacity	11/21 (52%)	6/33 (18%)	$P \leqslant 0.02$
Microscopic haematuria	2 (6%)	2 (5%)	NS
cU IgG (⩾ 5.0 μg/min)	8 (24%)	3 (7%)	NS
cU albumin (⩾ 20 μg/min)	9 (26%)	0	$P \leqslant 0.01$
cU α1-microglobulin (⩾ 7.0 μg/min)	7 (21%)	2 (5%)	NS
ANA positive	28 (82%)	38 (86%)	NS
SS-A positive	25 (76%)	32 (73%)	NS
SS-B positive	21 (64%)	20 (46%)	NS
Serum IgG (g/l)	19.7 ± 7.7	18.3 ± 6.6	NS
Serum β2m (mg/l)	3.33 ± 1.71	2.73 ± 0.77	$P \leqslant 0.025$

Renal Involvement and Followup of 130 Patients with Primary Sjögren's Syndrome

The Journal of Rheumatology 2008.

HON REN

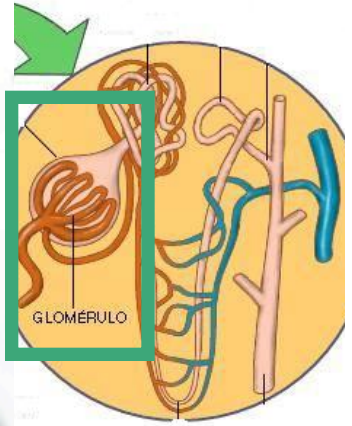
- **Densidad** urinaria<1010 (tras deprivación) + pHo>7 x 6m
- **CRU** nefrolitiasis/nefrocalcinosis recurrente
- Sd. **Fanconi**
- **Creat** > 1.4 o GFR<50 ml/min
- **Proteinuria**>0.5g/d x 3m
- **Sedimento** activo

N=130 (1993-2006)

Variable	IN, n = 99	GN, n = 18	p
Age, mean, yrs	43.41 ± 11.74	44.11 ± 12.22	NS
Duration of the disease, yrs	2.69 ± 4.99	3.94 ± 4.54	NS
Dry mouth, % (n)	87.5 (77/88)	93.3 (14/15)	NS
Dry eyes, % (n)	72.7 (64/88)	86.7 (13/15)	NS
Serum creatinine, μmol/l	114.18 ± 90.52	145.86 ± 183.43	NS
Anti-SSA-positive, % (n)	52.1 (49/94)	38.9 (7/18)	NS
Anti-SSB-positive, % (n)	39.8 (37/93)	27.8 (5/18)	NS
Serum IgG, g/l	2187.02 ± 927.29	2410.28 ± 1414.48	NS
RF, % (n)	54.3 (38/70)	64.7 (11/17)	NS
Low C3, % (n)	45.6 (49/90)	17.6 (3/17)	< 0.05
Low C4, % (n)	13.2 (12/91)	11.8 (2/17)	NS
Increased ESR, % (n)	71.3 (67/94)	64.7 (11/17)	NS
Cryoglobulins	0	0	

Daño **Glomerular** SSp **5%**

¿Posibilidad de desarrollar **ERC**?

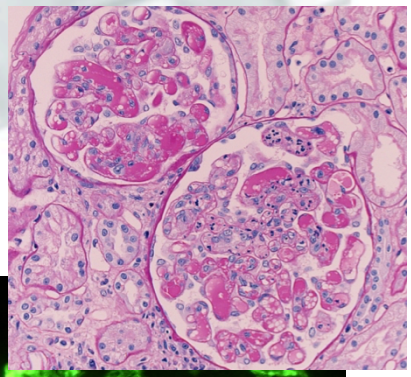


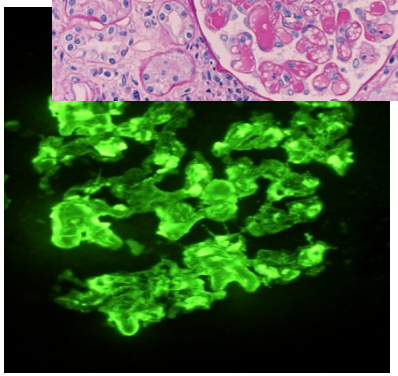
- Muy INFRECUENTE
- Etiología: depósito de **inmunocomplejos/crioglobulinas**.
- AP: **GN proliferativa ± trombos hialinos** 5-30%
  (**Membranoproliferativa, Crioglobulinémica)**

  Membranosa (3-15%), **Mesangial IgA** (7-21%)

  GNCM 4%, **GEFS** (1.5-8%),

  GN Extracapilar (aislados) …



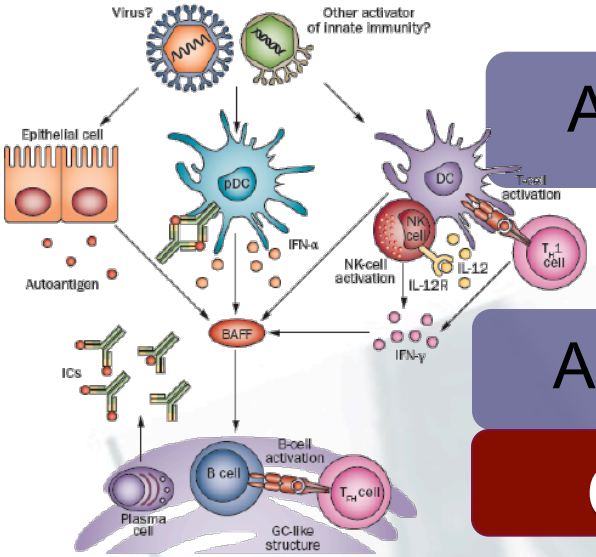


- Clínica: Sd.Nefrítico > Nefrótico

  ↓↓ C_4, Crios+

- → → → **Linfoma (2-9%)**

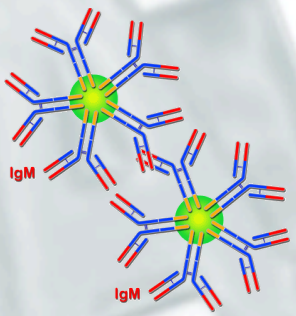
Crioglobulinemia & SSp



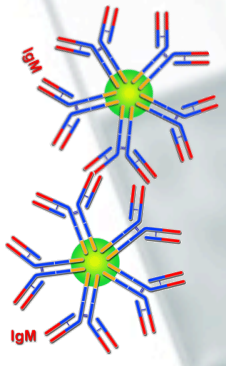
Activación policlonal de LB

Activación oligoclonal de LB

CRIOGLOBULINAS

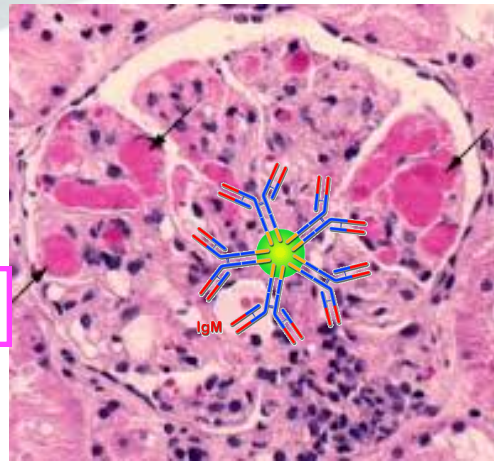


Prevalencia: 13-16%



Asociación con:

- **Fenómeno Raynaud**
- **Púrpura**
- **Polineuropatía**
- **Glomerulonefritis 28%**
- **Linfoma: 38%**



Estado Prelinfomatoso

Clinically Significant Renal Involvement in Primary Sjögren's Syndrome

ARTHRITIS & RHEUMATISM
2013,

Andreas V. Goules

Clinical, immunologic, and laboratory parameters	Interstitial nephritis (n = 13)	GN (n = 22)	P†
Age at onset of renal involvement, mean ± SD years	42.38 ± 15.16	47.55 ± 10.35	0.374
Primary SS disease duration prior to renal involvement, mean ± SD years	2.75 ± 3.33	7.08 ± 5.28	0.008
Dry eyes	11/13	21/22	0.541
Dry mouth	13/13	21/22	1.000
Parotid enlargement	6/13	11/22	1.000
Lung involvement	2/13	3/22	1.000
Thyroid involvement	3/13	2/22	0.337
Arthralgias/arthritis	10/13	17/22	1.000
Raynaud's phenomenon	6/13	13/22	0.503
Liver involvement	1/13	2/22	1.000
Peripheral neuropathy	3/13	5/22	1.000
Purpura	5/13	10/22	0.332
Lymphoma	1/13	8/22	0.109
Anti-Ro	10/13	14/22	0.478
Anti-La	7/13	8/22	0.481
Rheumatoid factor	9/13	13/22	0.721
Hyperglobulinemia‡	5/10	9/17	1.000
Cryoglobulins‡	2/13	14/22	0.013
Low C3‡	0/13	9/22	0.013
Low C4‡	5/13	14/22	0.179
Proteinuria‡	1/13	19/22	0.0001
Active urine sediment‡	0/13	15/22	0.0001
Nephrolithiasis‡	3/13	3/22	0.649
Renal failure‡	6/13	5/22	0.258

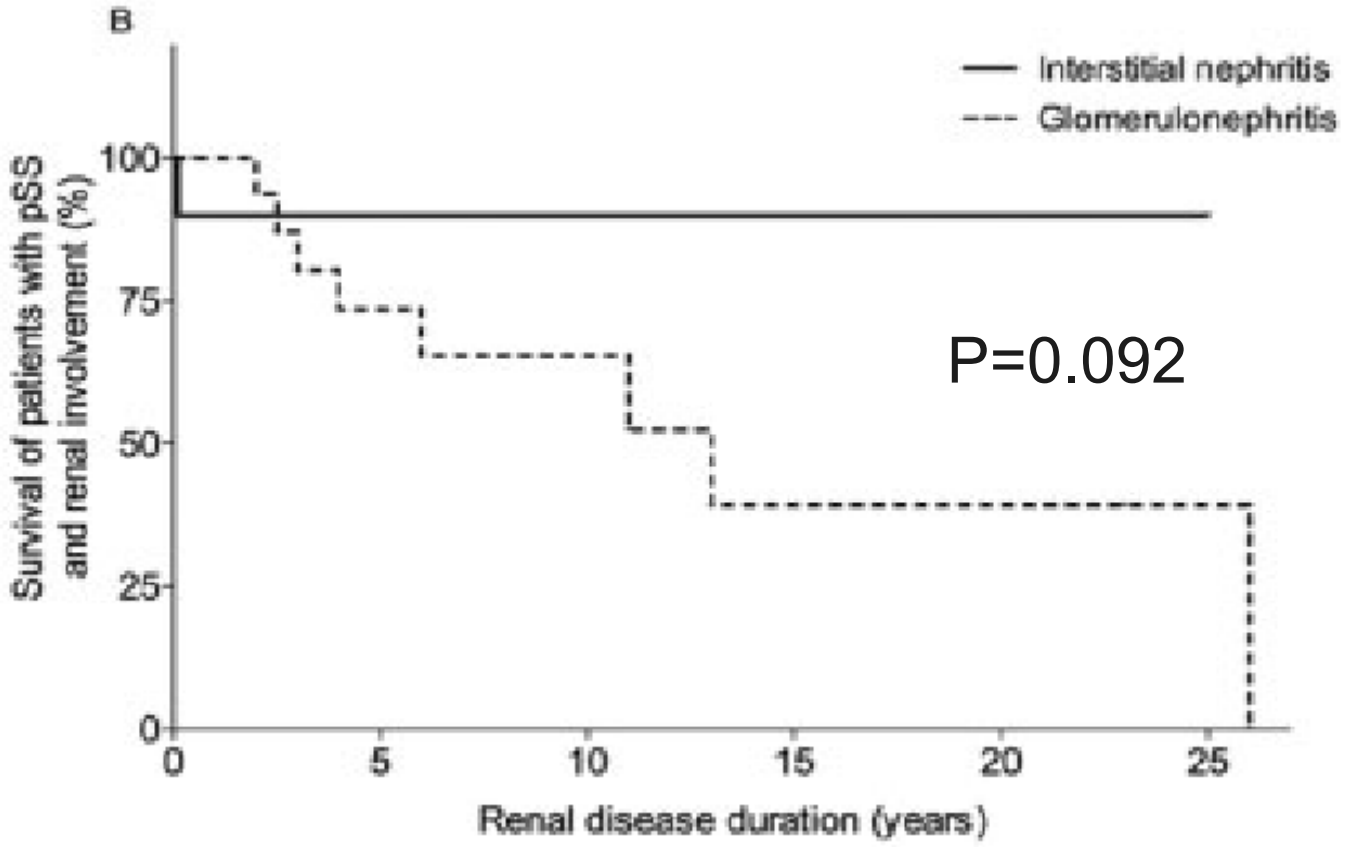
Clinically Significant Renal Involvement in Primary Sjögren's Syndrome

ARTHRITIS & RHEUMATISM
2013.

Andreas V. Goules

N=35/715 (5%) seguimiento 252 pacientes-año

PRONÓSTICO Supervivencia Paciente



P=0.092

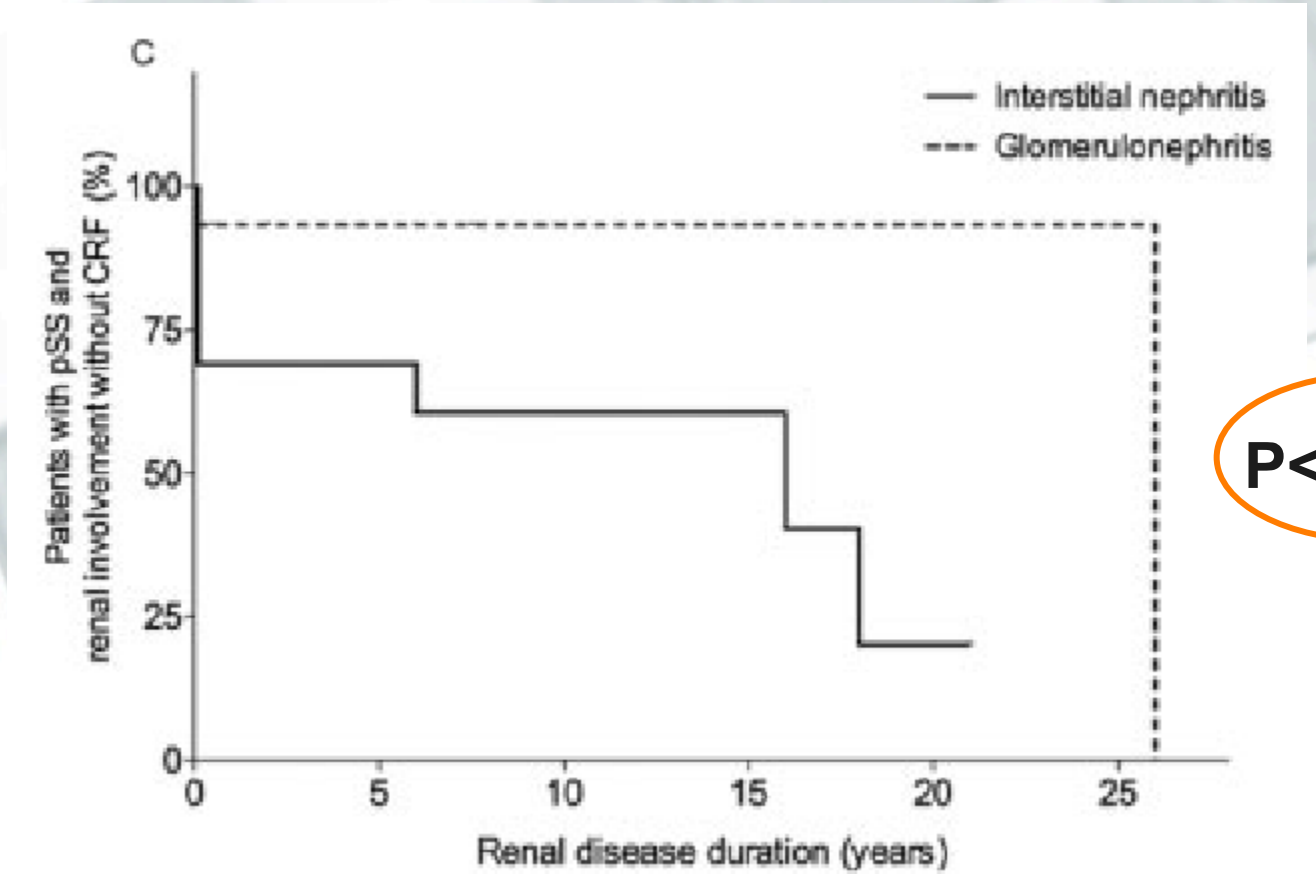
Clinically Significant Renal Involvement in Primary Sjögren's Syndrome

ARTHRITIS & RHEUMATISM
2013.

Andreas V. Goules

N=35/715 (5%) seguimiento 252 pacientes-año

PRONÓSTICO Supervivencia Renal



P<0.037

Clinical and morphological features of kidney involvement in primary Sjögren's syndrome

Nicola Bossini[1], Silvana Savoldi[1], Franco Franceschini[2],

Nephrology Dialysis Transplantation
2001

- N= 16/**60 (27%)** pacientes SSp.

	Number of patients	%
Renal failure	8	13
Metabolic acidosis	3	5
Hypokalaemia	4	7
Morning urine pH >5.5	23	38
Complete dRTA	3	5
Morning urine osmolarity less than normal age-related value mOsm/Kg	39	66
Proteinuria <1 g/24 h	9	15
Proteinuria 1.5–2 g/24 h	1	2
Nephrotic proteinuria	2	3
Microscopic haematuria associated with proteinuria	5	8
Glycosuria	0	0
Urinary concentrating defect associated with GFR reduction	5/48*	10
Urinary concentrating defect associated with normal GFR	5/48*	10
Isolated urinary concentrating defect	3/48*	6

Clinical and morphological features of kidney involvement in primary Sjögren's syndrome

Nicola Bossini[1], Silvana Savoldi[1], Franco Franceschini[2],

Nephrology Dialysis Transplantation 2001

- N= 16/**60 (27%)** pacientes SSp→ **9 BIOPSIAS**:

- 6 (67%) **NTI**.
- 3 (33%) **GN:** 1 GN MB (NTI)
  1 GNMSG C3 (NTI),
  1 GNMP crioglobulinémica

Correlación Clínico-Patológica

	GFR (ml/min/1.73m²)	Proteinuria (gr/día)	Hematuria (si/no)
6 **NTI**	< 65	0.3-0.7	50%
3 **GN**	75-100	2-10	75%

Renal Involvement in Primary Sjögren Syndrome: a clinicopathological study

Maripuri S, Donadio, Fervenza (Mayo Clinic CJASN 2009)

- N= **24** biopsias renales en **7276** SSp (1967-2007)

Table 1. Clinical and laboratory features in 24 patients with primary Sjogren's syndrome and renal involvement

Baseline Characteristics and Classification Criteria	Number/Total	Percent
Female gender	21/24	83
Dry eyes	22/24	92
Dry mouth[a]	19/24	79
Positive for SSA or SSB	15/18	83
Positive for RF	16/20	80
Positive Schirmer's test or Rose Bengal score >4	11/12	92
Positive lip biopsy[b]	1/3	33
Clinical renal presentation		
acute renal failure	7/24	29
stage IV or V chronic kidney disease	10/24	42
hemodialysis	1/24	4
Associated findings of renal disease		
RTA	8/24	33
proteinuria	16/24	67
intermediate range proteinuria (0.3 to 1.5 g/24 h)	14/16	88
nephrotic range proteinuria (>1.5 g/24 h)	2/16	13
history of renal calculi	4/24	17
cryoglobulins	3/24	13
Medical comorbidities		
diabetes mellitus	3/24	13
hypertension	12/24	50

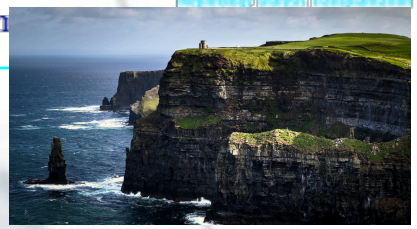
Renal Involvement in Primary Sjögren Syndrome: a clinicopathological study

Maripuri S, Donadio, Fervenza (Mayo Clinic CJASN 2009)

- N= **24** biopsias renales en **7276** SSp (1967-2007)
- "*because **chronic TIN** with **monolymphocytic infiltrate** is the prototypic renal lesion in pSS, we propose that a **KB** desmonstrating these findings should also be considered as an additional supportive **criterion to the classification criteria for pSS***".
- 4 (17 %) **LINFOMA** LEB, MALT (3 Ghost, 1 sarcoidosis).

Kidney biopsy findings in primary Sjögren syndrome

Dana Kidder[1], Elaine Rutherford[2], David Kipgen[3], Stewart Fleming[4], Colin Geddes[2] and Grahan

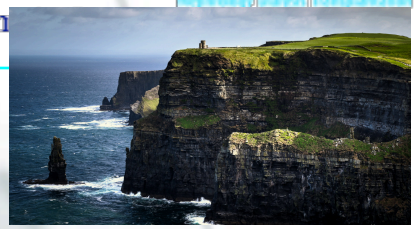


- N= **25** biopsias renales (1978-2013).

	All cases	TIN	GN	P-value
Median age (range)	55 (26–82)	55 (26–65)	63 (31–82)	0.3
Sex female/male	22/3	12/1	7/2	0.5
Median duration of disease in patients with known PSS diagnosis prior to renal biopsy in years (range)	5 (1–21)	5.5 (1–12)	8.5 (2–11)	0.6
Median duration of follow-up (range)	36 (0.5–288) months	80 (4–288)	22 (0.5–180)	0.11
Arthralgia/arthritis (%)	11/25 (49)	8 (61)	3 (33)	0.4
Cutaneous (%)	7/25 (27.5)	3 (23)	3 (33)	0.65
Interstitial lung disease (%)	5/25 (17)	1 (7.6)	3 (33)	0.3
Raynaud's phenomenon (%)	3/25 (10)	1 (7.6)	1 (3.7)	1.0
Pericarditis (%)	1/25 (3)	0	0	–
Proteinuria >0.3 g per 24 h (%)	19/25 (76)	3 (23)	9 (100)	0.0005
Proteinuria >1 g per 24 h (%)	13/25 (40)	2 (15)	9 (100)	0.0002
Proteinuria >3 g per 24 h (%)	7/25 (28)	1 (7)	7 (77)	0.001
Microscopic haematuria (%)	13/23 (56)	5 (38)	7 (77)	0.09
GFR 60 mL/min/1.73 m^2 (range)	26 (5–150)	28 (5–67)	39 (6–150)	0.2
eGFR <60 mL/min/1.73 m^2 (%)	21/25 (84)	11 (84)	9 (77)	0.6
eGFR <30 mL/min/1.73 m^2 (%)	14/25 (56)	7 (54)	5 (38)	1.0
Hypokalemia <3.5 mmol/L (%)	3/29 (10)	3 (23)	0	-
Low serum bicarbonate <22 mmol/L (%)	12/25 (52)	6 (48)	4 (44)	1.0
Anti-nuclear antibody positive (%)	17/23 (74)	9/12 (75)	6 (66)	1.0
Anti-Ro/La antibody positive (%)	12/19 (63)	8 (61)	4 (44)	0.6
Rheumatoid factor positive (%)	10/19 (52)	4 (30)	6 (66)	0.2
Raised serum IgG (>12 g/L)	12/18 (66)	8/12 (66)	4/8 (50)	0.6
Raised CRP (>6 mg/L)	12/20 (60)	7 (54)	5 (55)	1.0

Kidney biopsy findings in primary Sjögren syndrome

Dana Kidder[1], Elaine Rutherford[2], David Kipgen[3], Stewart Fleming[4], Colin Geddes[2] and Grahan



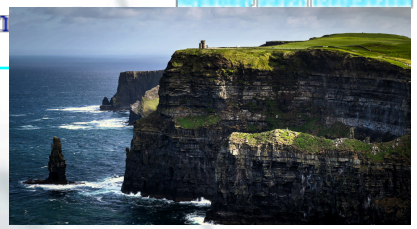
- N= **25** biopsias renales (1978-2013).
- 9/25 (36%) **GN**:
  - 6 **GNMP** (1 Crio, 2 NTI)
  - 1 **GNMB** (NTI)
  - 1 **GN IgA**
  - 1 **Cambios Mínimos**
  - 1 **ANCA-MPO**
- 12/25 (48%) **NTI**: 12 **NTI (2 nefrocalcinosis, 1 sarcoidosis)**
- 3 (12%) OTROS: N.DM, NTA, N.RVU

Correlación clínico-patológica

- **SdNefrótico**: 6 GN, 1 NTI
- **Sd.Hematuria-Proteinuria**: 6 GN, 4 NTI, 1 NTA
- **Hematuria aislada**: 1 NTI.
- **Hipocalemia** 1 GN, 2NTI
- **eGFR 39**ml/min/1.73m^2 (GN), **28**ml/min/1.73m^2 (NTI)

Kidney biopsy findings in primary Sjögren syndrome

Dana Kidder[1], Elaine Rutherford[2], David Kipgen[3], Stewart Fleming[4], Colin Geddes[2] and Grahan

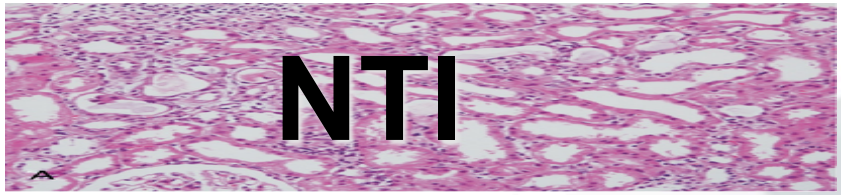


- N= **25** biopsias renales (1978-2013).

Clinical outcomes	All cases	TIN	GN	P-value
3-Year patient survival %[a]	88	100	66	0.02
3-Year renal survival %[a]	93	92	92	1.0
RRT at presentation (%)	4/25 (13)	2/13 (15)	2/9 (15)	1.0
Complete remission[b] (%)	12/22 (54)	7/13 (46)	3/9 (22)	0.4
Stable reduced renal function (%)	6/22 (27)	2/13 (23)	4/9 (30)	0.2
Progressive deterioration in renal function (%)	8/22 (15)	4/13 (7)	2/9 (10)	1.0
Malignancies (%)	6/22 (27)	5/13 (38)	1/9 (20)	0.3
Lymphoma (%)	4/22 (18)	3/13 (23)	1/9 (10)	0.6

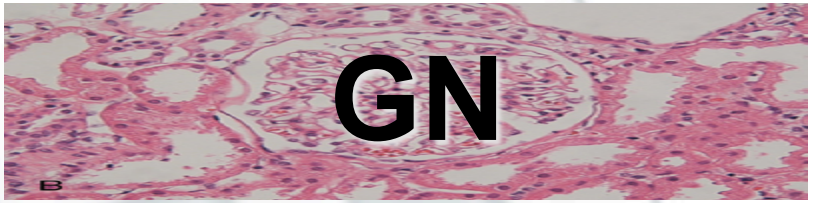
Study	Patients	Number of patients with renal biopsy	Follow-up months (range)	TIN (percentage out of total biopsies)	GN (percentage out of total biopsies)	Combined GN+TIN	Number of patients reaching ESRD (percentage out of total patients biopsies)	Number of patients with lymphoma
Goules *et al.* [9]	715	35	0–312	13	17	5 (considered as GN)	4 (11.4%)	9 (25.7)
Lin *et al.* [4]	573	64	NA	21	23	18	NA	NA
Maripuri *et al.* [7]	24	24	76 (17–192)[a]	17 (71)	4 (16.6)	2 (considered as TIN)	0	4 (17%)
Ren *et al.* [5]	130	41	6–120	33 (80.5)	8 (19.5)	0	4 (9.75%)	1
Bossini *et al.* [6]	60	9	NA	6 (66)	3 (33)	0	NA	NA
Goules *et al.* [8]	20	18	120	10 (55)	8	4 (considered as GN)	4 (20%)	2 (10)

Afectación Renal en el SSp



NTI

- **Frecuente** (22-30%)
- **Temprano** en la evolución del SSp
- **Infiltrac**. túbulointersticial L.T(CD4+)-Cels.plasmáticas
- **Latente**: ATR, Fanconi
- Dx: **sg y orina** (pH-Bic, Glu, P, AU, aa, $\beta_2$microglobulina), +/- **Bx si IR**
- Tto: **electrolitos** +/- GC/IS.
- Pronostico: "**bueno**"



GN

- **Rara** (<5-10%)
- **Tarde** en la evolución del SSp (púrpura, SNP…)
- **Depósito** de IC/Crios.
- **Florida**:Sd.Nefrótico/ítico
- Dx: **Biopsia**

  ↓↓ C_4, Crios+
- Tto: **IS**
- Pronóstico: "**peor**" (SLP)

Factores Predictores de afectación renal en el SSp

- 55 pacientes con (18) / sin (37) alter.**acidificación**
- 78 pacientes con (34) / sin (44) **proteinuria** >0.15gr/d, con (9) / sin(69) **α1 microglobinuria**>7ug/min.

- Seguidos durante 57 ± 13 años.

- FR +, $\beta_2$uglobulinemia ↔ α1uglobinuria
- Prot.totales, γglobulinas sg↔ Acidificación

Clinical Nephrology 2001

- FR **Glomerulonefritis**:
  - Crioglobulinemia
  - C4 bajo
  - Púrpura

AR 2000

EULAR Sjogren's Syndrome Disease Activity Index: development of a consensus systemic disease activity index for primary Sjogren's Sd

Raphaèle Seror… on behalf of the EULAR Sjögren's Task Force

Ann Rheum Dis. 2010;69:1103–1109

Domain [Weight]	Activity level	Description
Pulmonary [5] *Rate as "No activity" stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use etc.)*	No =0	Absence of currently active pulmonary involvement
	Low = 1	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: No breathlessness and normal lung function test.
	Moderate = 2	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% >DL_{CO}≥ 40% or 80%>FVC≥60%
	High = 3	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: DL_{CO}< 40% or FVC< 60%
Renal [5] *Rate as "No activity" stable long-lasting features related to damage, and renal involvement not related to the disease.* *If biopsy has been performed, please rate activity based on**histological**features first*	No = 0	Absence of currently active renal involvement with proteinuria< 0.5 g/d, no hematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 1	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/d) and without hematuria or renal failure (GFR ≥60 ml/min)
	Moderate = 2	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/d and without hematuria or renal failure (GFR ≥60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 3	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/d or hematuria or renal failure (GFR <60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement
Muscular [6] *Exclusion of weakness due to corticosteroids*	No = 0	Absence of currently active muscular involvement
	Low = 1	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N <CK ≤ 2N)
	Moderate = 2	Moderately active myositis proven by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK ≤4N),
	High = 3	Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤ 3/5) or elevated creatine kinase (>4N)
PNS [5] *Rate as "No activity" stable long-lasting features related to damage or PNS involvement not related to the disease*	No = 0	Absence of currently active PNS involvement
	Low = 1	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia
	Moderate = 2	Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia,

Arthritis & Rheumatism 2008;56:2223–2231

Sjogren's Syndrome Disease Damage Index and Disease Activity Index

Scoring System for the assessment of Disease Damage and Diseas Activity in Sjögren´s Syndrome, Derived From an Analysis of a Cohort of Italian Patients

Table 2. Sjögren's Syndrome Disease Damage Index*

Item	Definition	Score
Oral/salivary damage		
Salivary flow impairment	Unstimulated whole saliva collection <1.5 ml/15 minutes, by standard method†	1
Loss of teeth	Complete or almost complete	1
Ocular damage		
Tear flow impairment	Schirmer I test <5 mm in 5 minutes, by standard method†	1
Structural abnormalities	Corneal ulcers, cataracts, chronic blepharitis	1
Neurologic damage		
CNS involvement	Long-lasting stable CNS involvement	2
Peripheral neuropathy	Long-lasting stable peripheral or autonomic system impairment	1
Pleuropulmonary damage (any of the following)		2
Pleural fibrosis	Confirmed by imaging	
Interstitial fibrosis	Confirmed by imaging	
Significant irreversible functional damage	Confirmed by spirometry	
Renal impairment (any of the following)		2
Increased serum creatinine level or reduced GFR	Long-lasting stable abnormalities	
Tubular acidosis	Urinary pH >6 and serum bicarbonate <15 mmoles/liter in 2 consecutive tests	
Nephrocalcinosis	Confirmed by imaging	
Lymphoproliferative disease (any of the following)		5
B cell lymphoma	Clinically and histologically confirmed	
Multiple myeloma	Clinically and histologically confirmed	
Waldenström's macroglobulinemia	Clinically and histologically confirmed	

Tratamiento en SSp

- Afectación renal en el SSp: en su mayoría curso benigno → *sólo un **pequeño grupo de pacientes** requerirán intervención terapéutica para impedir o retrasar la ERC.*
- Pocos estudios sobre tratamiento (series de casos)

- **ATR:** potasio, Bicarbonato…
- **NTIA**: corticoterapia*
- **NTIC**: corticoterapia*
- **GN**: inmunosupresión GC+CF/MMF/AZT/RTX

**Se ha probado IS mayores pero no clara evidencia. Se reservan para no respuesta con o necesidad de ahorrar GC*

Tratamiento en SSp

Table 3 | **Treatment of renal disease in primary Sjögren syndrome**

Study	Renal disease treatment	Number of patients treated	Renal disease (*n*)	Clinical response (*n* response/total)
Ren *et al.* (2008)[22]	Steroids and immunosuppressants	41	TIN (33), MS (3), MPGN (2), FSGS (2), MN (1)	Remission (18/33) Improved renal function (7/33)
Maripuri *et al.* (2009)[21]	Prednisone alone	9	FSGS with TIN (1)	eGFR improvement (1/1)
			MPGN (1)	Insufficient follow-up (1/1)
			TIN (7)	Stable eGFR (3/7) and eGFR improvement (4/7)
	Hydroxychloroquine and prednisone	6	MPGN (1)	Improved GFR (1/1)
			MC (1)	Improved GFR (1/1)
			TIN (4; 1 with FSGS)	Improved GFR (3/4), insufficient follow-up (1/4)
	Cyclophosphamide and prednisone	2	TIN (2)	Stable eGFR (2/2)
	Prednisone and rituximab	1	TIN (1)	eGFR improvement (1/1)
	Prednisone and PE	2	TIN (2)	Stable eGFR (2/2; 1 remained in TRF)
Goules *et al.* (2013)[25]	Steroids alone	5	MS (2), MN (1), MPGN (2)	Remission (5/5)
	Cyclophosphamide and steroids	9	MS (3), MPGN (6)	Remission (7/9), TRF (2/
	Steroids and Aza–CyA	2	MS (1), MN (1)	Remissi
	Rituximab	1	MS (1)	
	Potassium bicarbonate supplement	12	TIN (12)	Tl
Gottenberg *et al.* (2013)[56]	Rituximab on top of steroids and other immunosupressants	6	Unknown (6)	Ren

Clinically Significant and Biopsy-Documented Renal Involvement in Primary Sjögren Syndrome.

Goules A. Medicine 2000

TABLE 1. Initial clinical, laboratory and imaging abnormalities; histopathology; and outcome of patients with renal disease

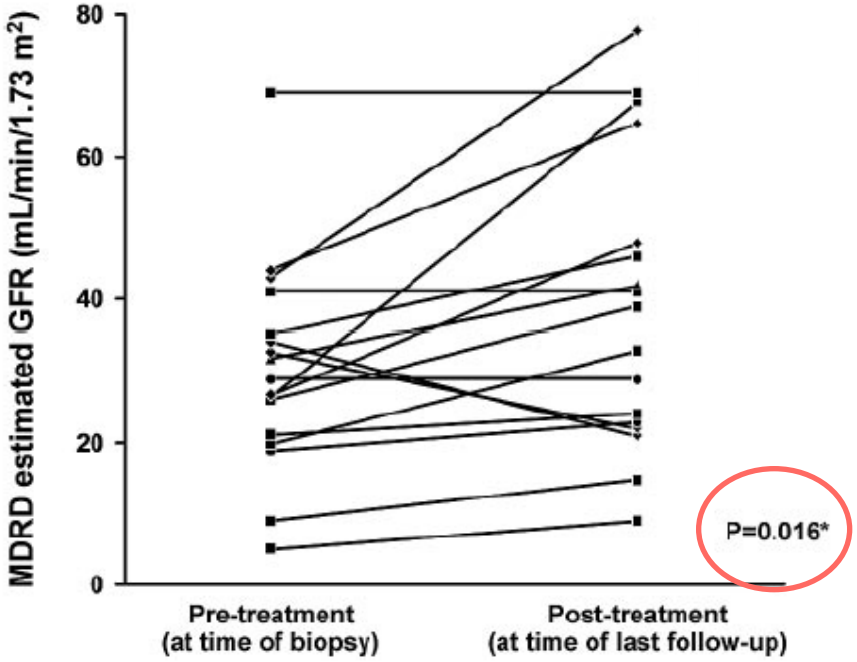
Patient	Clinical Manifestation	Blood Examination	Urine Abnormality	Imaging Abnormality	Biopsy	Outcome of Renal Disease (Last Follow-Up Since Onset)
1	None	Cr: 1.0	sg<1010, pH>7	None	IN	Cr: 1.3 (0.3 yr)
2	Renal colics	Cr: 0.8	sg<1010, pH>7	Urolithiasis	IN	Cr: 0.9 (8 yr)
3	Renal colics	Cr: 1.2	sg<1010, pH>7	Urolithiasis	IN	Cr: 1.4 (13 yr)
4	None	Cr: 2.2	sg<1010, pH>7	None	IN	Cr: 1.3 (2 yr)
5	Polydipsia, polyuria, Nocturia	Cr: 1.8	sg<1010, pH>7	None	IN	Cr: 2.3 (6 yr)
6	None	Cr: 1.1	sg<1010, pH>7	None	IN	Cr: 1.2 (8 yr)
7	None				IN	Cr: 1.4 (0.1 yr)
8	None				IN	CRF, Cr: 2.0 CCl: 40 (3.5 yr)
9	None				IN	CRF, Cr: 2.0 CCl: 25 (13 yr)
10	Renal colics				Not done (presumably IN)	CRF, Cr: 3.2 CCl:20 (23 yr)
11	Hypertension, Periorbital edema				MP GMN (IgM and C3 deposition)	Cr: 0.8 (6 yr)
12	None				MS GMN	Cr: 1.0 (2 yr)
13	None				MP GMN	CRF, Cr: 5.9, hemodialysis (1
14	None				MP GMN (IgM and C3 deposition)	Cr: 1.2 (2
15	None	Cr: 1.0	Proteinuria	None	MS GMN	
16	None	Cr: 1.1	Proteinuria, hematuria, red blood cell casts	None	MS GMN	
17	None	Cr: 1.5	Proteinuria	None	M	
18	Hypertension, periorbital edema	Cr: 1.5	Proteinuria, hematuria	None	MP C	
19	Renal colics	Cr: 6.2 CCl: 35 (at GMN onset)	sg<1010, pH>7 Proteinuria, hematuria, red blood cell casts	Urolithiasis	Not d (pre IN +	yr)
20	Hypertension	Cr: 1.6 (at GMN onset)	sg<1010, pH>7, proteinuria	None	IN + MI and C3 de	lost to follow-up)

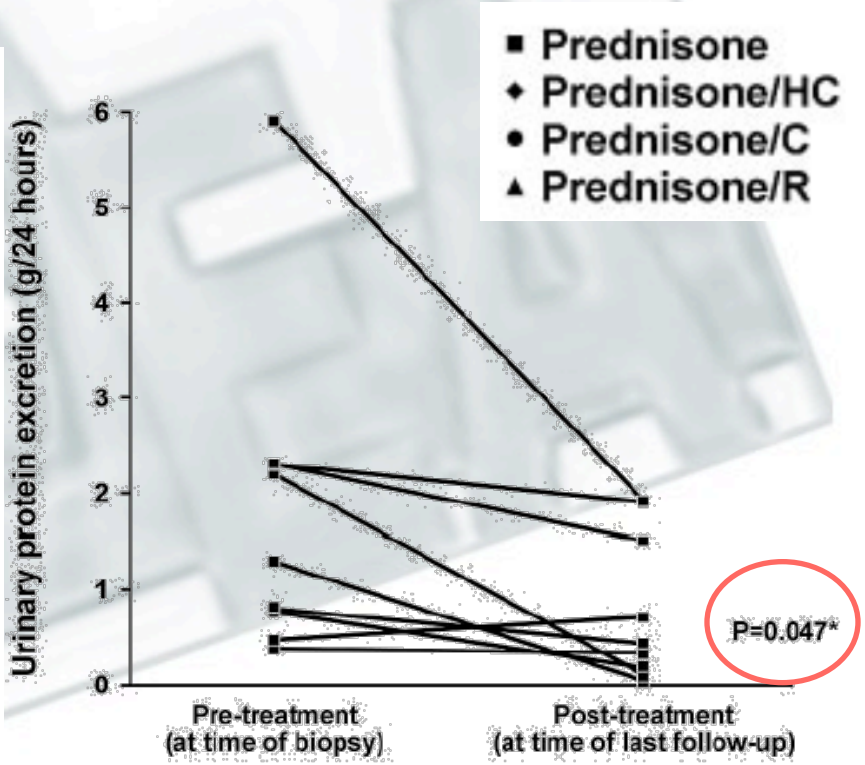
- **Potasio** (NTI)
- **CF+PF** (CME)
- GN (MSG y MP): **GC+CF**
  GC+AZT
  GC sólos

Renal Involvement in Primary Sjögren Syndrome: a clinicopathological study

Maripuri S, Donadio, Fervenza (Mayo Clinic CJASN 2009)

N=24 (NTI, GN). Seguimiento **76m** (17-192)



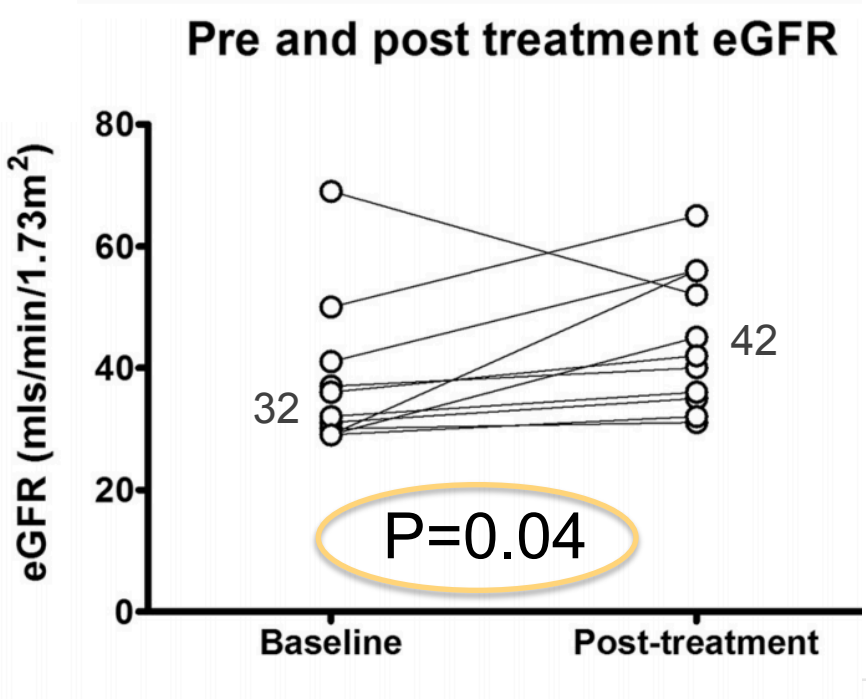


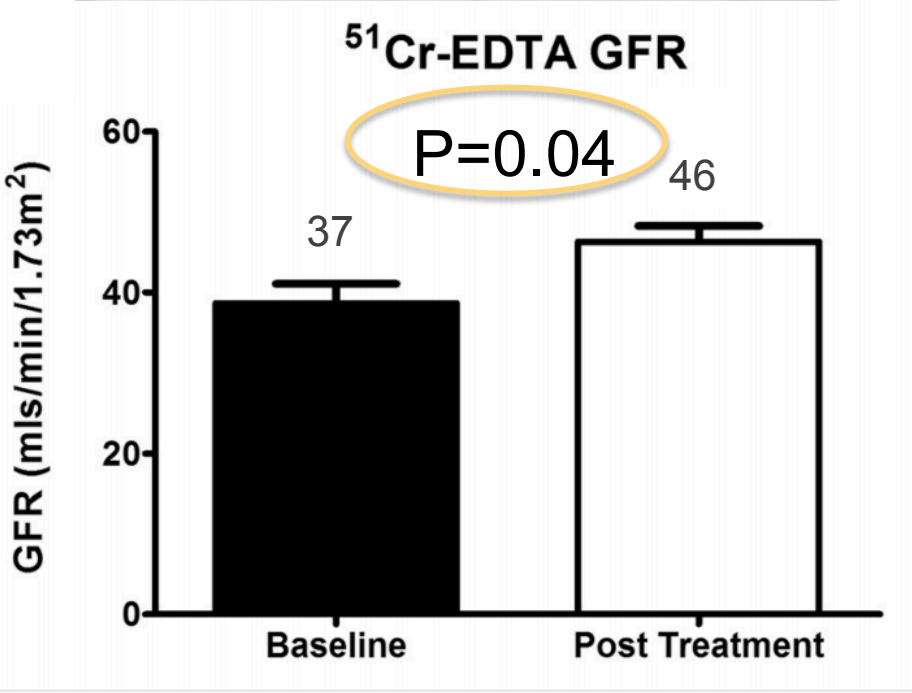
- 9 pacientes (56%) mantuvieron al menos un 30% de mejoría en el FG.
- 8 pacientes (42%) empeoraron pero se mantuvieron después estables.
- 2 pacientes (11%) deterioraron y progresaron a estadío III-IV

Tubulointerstitial Nephritis in primary Sjögren synd: clinical manifestations and response to treatment

Evans RD. BMC Musc Dis 2016

N=12 pacientes con NTI (bx), ATR tratados con **GC+MMF** 1-1.5gr/d (11)/**AZT** 63mg/d (2) 24m



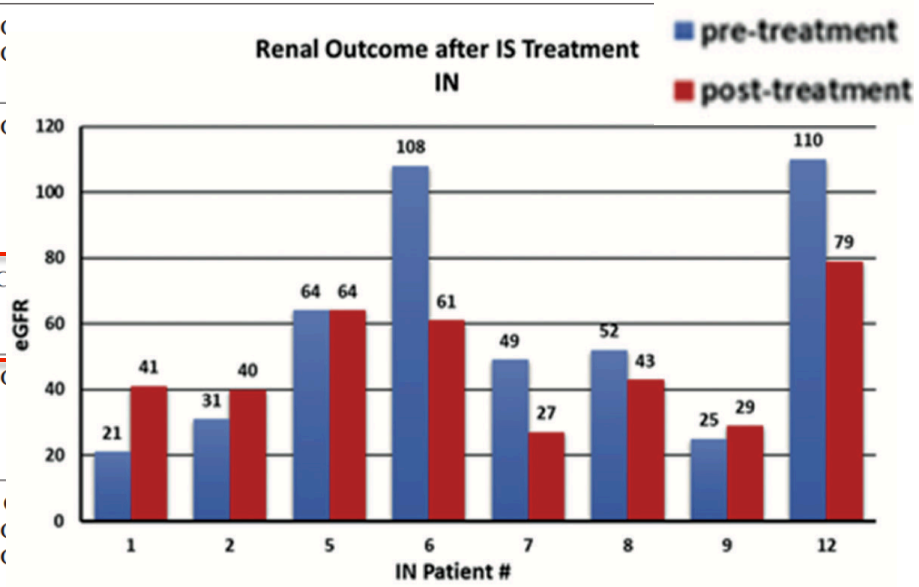


Renal involvement in primary Sjögren's syndrome: natural history and treatment outcome

Goules AV. Clin Exp Rheumatol 2019

Table III. Immunosuppressive treatment and renal outcome in pSS patients with IN.

Biopsy	Patient no.	Presentation	Treatment	Before	After	Comments
NTI	1	CRF	· Prednisone 60mg (2mo) · Prednisone 40-15mg + MMF 500 x 2 (4mo) · Prednisone 3mg + MMF 250x2 (maintenance)-4mo	· Cr=2.3, GFR=2 1 · Cr=1.4, GFR=38 · Cr=1.3, GFR=41	· Cr=1.4 (2mo), GFR=38 · Cr=1.1, GFR=50 (4mo) · Cr=1.3, GFR=41	· Cr:1.3-1.5 (at diagnosis) (ACEi, dehydration) · One dehydration episode: Cr:2.8→1.5
NTI	2	CRF	· MMF 500mg x 2 (2mo) · MMF 1g x 2 (3mo)	· C · C		
NTI	5	Hypokalaemic paralysis normal renal function	In 5-year period · Prednisone 50mg · AZA 200mg/d (1y) · MMF 3g/d (6m0) · Rituximab (1cycle)	· C		
ND	6	Symptomatic hypokalaemia	· Prednisone up to 20mg, HQ and MMF 3g/d (7years) · MTX (1y)	· C		
ND (Enf.Chron)	7	Severe hypokalaemia	· Prednisone +MTX (2y) · Infliximab (6mo) · Adalimumab+MTX (5years) · Certolizumab (7mo)	· C		
NTI	8	Cr=1.3, mild proteinuria and haematuria	· Prednisone 40mg/d (2mo) · Prednisone 60mg/d (short course/4ws) · MMF 2g/d(2mo)	· C · C · C		
NTI	9	CRF-nephrocalcinosis	· Prednisone 40-15mg/d (2mo) · Prednisone 15mg + MMF 500 x 2 (4mo)	· Cr=2.3, GFR=25 · Cr=2.0, GFR=29	· Cr=2.0, GFR=29 · Cr=2.0, GFR=29	· Cr=1.8 (at diagnosis) · Mild tubulitis
ND	12	Gross haematuria, renal stone disease	MMF 500mgx2→1gx2 (6mo)	· Cr=0.6, GFR=110	· Cr=0.8, GFR=79	· Cr=0.8-1.3, (GFR= 90-70) fluctuations of renal function and deterioration of renal function, pyelonephritis



Combination Cyclophosphamide/Glucocorticoids Provide Better Tolerability and Outcomes versus Glucocorticoids Alone in Patients with Sjogren's Associated Chronic Interstitial Nephritis

Shen Y Am J Nephrol 2017

2002-2016, N= 70 SSp + **NTIC** → **56 Corticoides** vs **14 Ciclofosfamida + GC**
(GC > 15mg/kg/d 3 m) (CF 0.6-0.8g iv mensual)

↑Igs, IR, Infiltración Inflamatoria (Bx)

- **Bx** (36)
- **Proteinuria tubular** (<1gr/d) +

Bajo PM (electroforesis)
α1μGlobulina
β2μGlobulina
Prot.Binding Retinol
N-Acetil-B-aminoglucosidasa

ATR: pHo >5.5 x 3 veces
Concentración Urinaria: Mosenthal/Deprivación agua.
Reabsorción Tubular: Orina (Electrolitos, Glu, aa)

A los 12 meses:

- DS en **eGFR** GC vs GC+CF **p=0.006** uni y multivariante
  Esta mejoría sólo se vió en aquellos con **IgGbasal ≥ 1560mg/dl**
  eGFR < 90ml/min/1.73
- **DS en α1μGlobulina** GC vs GC+CF **p=0.01**

Combination Cyclophosphamide/Glucocorticoids Provide Better Tolerability and Outcomes versus Glucocorticoids Alone in Patients with Sjogren's Associated Chronic Interstitial Nephritis

Shen Y Am J Nephrol 2017

2002-2016, N= 70 SSp + **NTIC → 56 Corticoides** vs **14 Ciclofosfamida + GC**

Table 1. Comparison of baseline characteristics and treatment efficacies between 2 therapeutic groups

Variables	CTX group (n = 14)	Steroid group (n = 56)	p value
Age, years	44.29±14.56	46.86±11.86	0.49
Female, n (%)	12 (85.7)	53 (94.6)	0.26
Hypertension, n (%)	5 (35.7)	14 (25.9)	0.51
Dry mouth, n (%)	12 (85.7)	42 (85.7)	1
Dry eyes, n (%)	9 (75)	34 (69.4)	1
SSA (+), n (%)	11 (78.6)	43 (76.8)	1
SSB (+), n (%)	12 (85.7)	30 (53.6)	0.028
IgG, mg/dL	2,705.39±1,446.68	2,334.43±708.15	0.39
Hb, g/L	107.31±16.63	114.79±18.01	0.18
Alb, g/L	38±4.49	38.11±3.75	0.93
RTA, n (%)	14 (100)	45 (80.4)	0.11
Baseline eGFR, mL/min/1.73 m^2	47.97±28.17	64.86±30.45	0.073
Positive for Uα1MG (≥1 MGtive)	13 (92.86)	35 (62.5)	0.062
Baseline InUα1MG, Gine	1.49	1.36	0.75
Hematological involvement, n (%)	4 (28.6)	19 (34.5)	0.76
Autoimmune thyroid diseases, n (%)	3 (25)	18 (50)	0.13
Interstitial lung disease, n (%)	1 (7.14)	3 (5.4)	1
Initial steroid dose, mg/day	28.57±7.95	25.67±9.02	0.28
Use of ACEI/ARB	7 (50)	15 (26.79)	0.18
~~Decline of serum IgG level, mg/dL~~	~~450 (910)~~	~~176 (1,910)~~	~~0.93~~
Improvement of eGFR, mL/min/1.73 m^2	21.35±19.63	2.72±19.11	0.006
Improvement of InUα1MG, mg/dL	1.66±0.70	0.40±1.35	0.01

Combination Cyclophosphamide/Glucocorticoids Provide Better Tolerability and Outcomes versus Glucocorticoids Alone in Patients with Sjogren's Associated Chronic Interstitial Nephritis

Shen Y Am J Nephrol 2017

2002-2016, N= 70 SSp + **NTIC → 56 Corticoides** vs **14 Ciclofosfamida + GC**

Table 2. Association between improvement of **eGFR** as a dependent variable with clinical characteristics, laboratory parameters, and therapeutic regimens as predictor variables

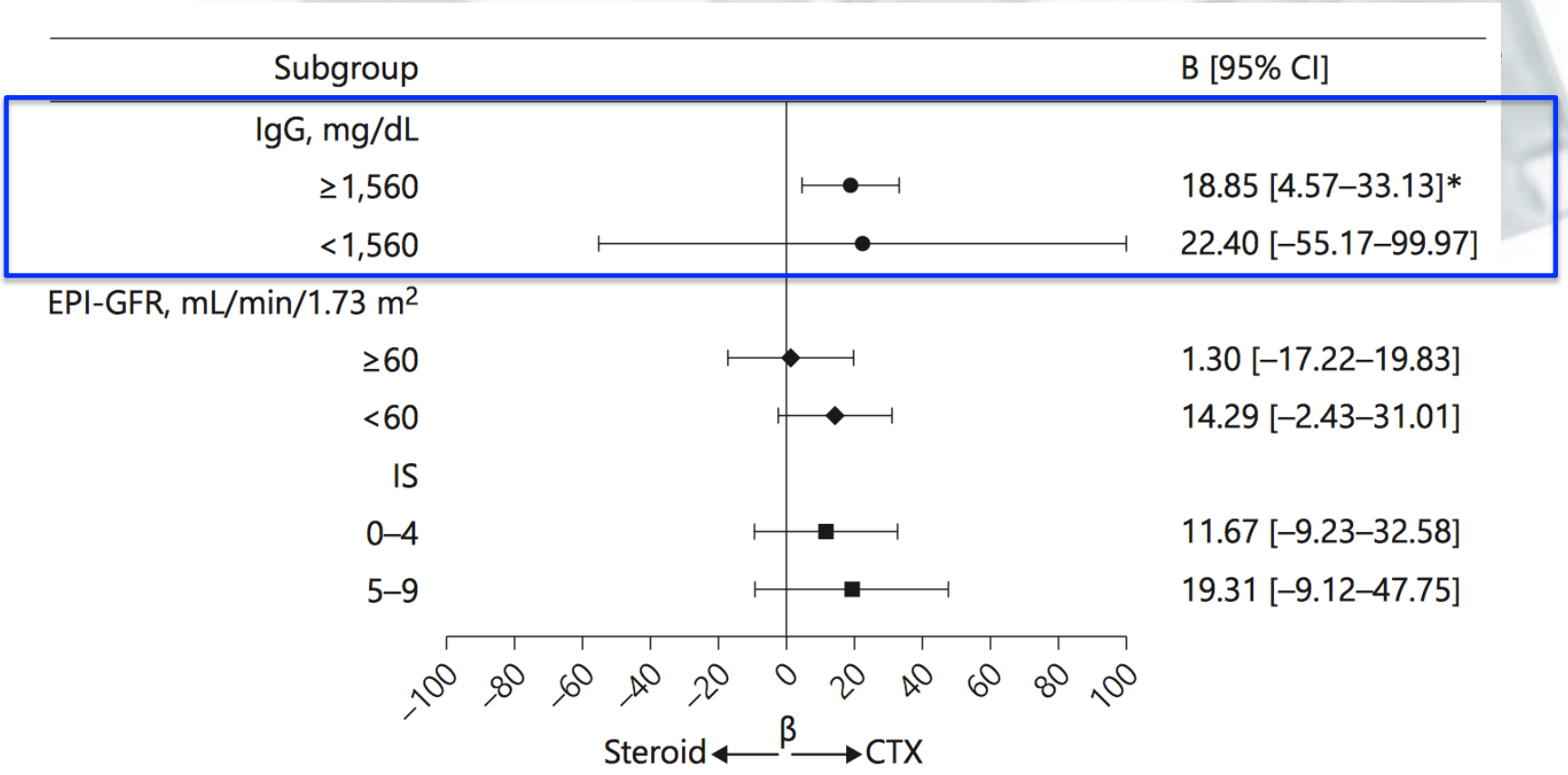
Predictor variable	Model 1 univariante		Model 2 **multivariante**	
	β	95% CI	β	95% CI
			*p<0.05, **p<0.01, ***p<0.001	
Age, years	−0.14	−0.61 to 0.33		
Gender, female	−4.2	25.63 to 17.23		
Hypertension, >140/90 mm Hg	0.9	−11.49 to 13.29		
Dry mouth	−21.78	−37.15 to −6.42**	−16.83	−28.22 to −5.45**
Dry eyes	−4.32	−16.63 to 7.99		
SSA (+)	−20.28	−32.15 to −8.42**	−3.5	−14.73 to 7.64
SSB (+)	−13.2	−24.03 to −2.37*	−7.38	−16.91 to 2.16
IgG, mg/dL	0.001	−0.006 to 0.008		
Hb, g/L	−0.5	−0.79 to −0.22**	−0.3	−0.52 to −0.07*
Alb, g/L	−1.31	−3.04 to 0.42		
RTA	0.72	−13.71 to 15.15		
Beseline eGFR, mL/min/1.73 m^2	−0.37	−0.52 to −0.22***	−0.21	−0.36 to −0.05*
Haematological involvement, *n*	−3.22	−14.78 to 8.34		
Autoimmune thyroid diseases, *n*	−11.54	−24.77 to 1.7		
Interstitial lung disease, *n*	−10.83	−40.46 to 18.81		
initial steroid dose, mg/day	1.2	0.62 to 1.78***	0.44	−0.03 to 0.92
Total CTX dose	−2.09	−7.84 to 3.66		
Use of ACEI/ARB	1.01	13.24 to 11.22		
CTX vs. steroid	18.63	5.68 to 31.58**	12.96	2.95 to 22.97*

Combination Cyclophosphamide/Glucocorticoids Provide Better Tolerability and Outcomes versus Glucocorticoids Alone in Patients with Sjogren's Associated Chronic Interstitial Nephritis

Shen Y Am J Nephrol 2017

2002-2016, N= 70 SSp + **NTIC → 56 Corticoides** vs **14 Ciclofosfamida + GC**

Fig. 1. Subgroup analyses. All results presented were calculated by linear regression. CI, confidence interval; CTX, cyclophosphamide; IgG, immunoglobulin G; IS, interstitial score *p<0.05



Combination Cyclophosphamide/Glucocorticoids Provide Better Tolerability and Outcomes versus Glucocorticoids Alone in Patients with Sjogren's Associated Chronic Interstitial Nephritis

Shen Y Am J Nephrol 2017

2002-2016, N= 70 SSp + **NTIC → 56 Corticoides** vs **14 Ciclofosfamida + GC**

Table 3. Association between improvement of **urine lnα1MG,** as dependent variable, with age, gender, baseline urine lnα1MG, and therapeutic regimens as predictor variables

	Model 1 univariante		Model 2 **multivariante**	
	β	95% CI	β	95% CI
Age, years	−0.01	−0.06 to 0.03	0.01	−0.02 to 0.05
Gender, female	0.04	−1.61 to 1.69	0.53	−0.62 to 1.68
Baseline InUα1MG, mg/dL	0.86	−0.06 to 0.03***	0.83	0.47 to 1.18***
CTX vs. steroid	1.26	0.33 to 2.18**	1.29	0.56 to 2.02**

*p<0.05, **p<0.01, ***p<0.001

EFECTOS ADVERSOS:

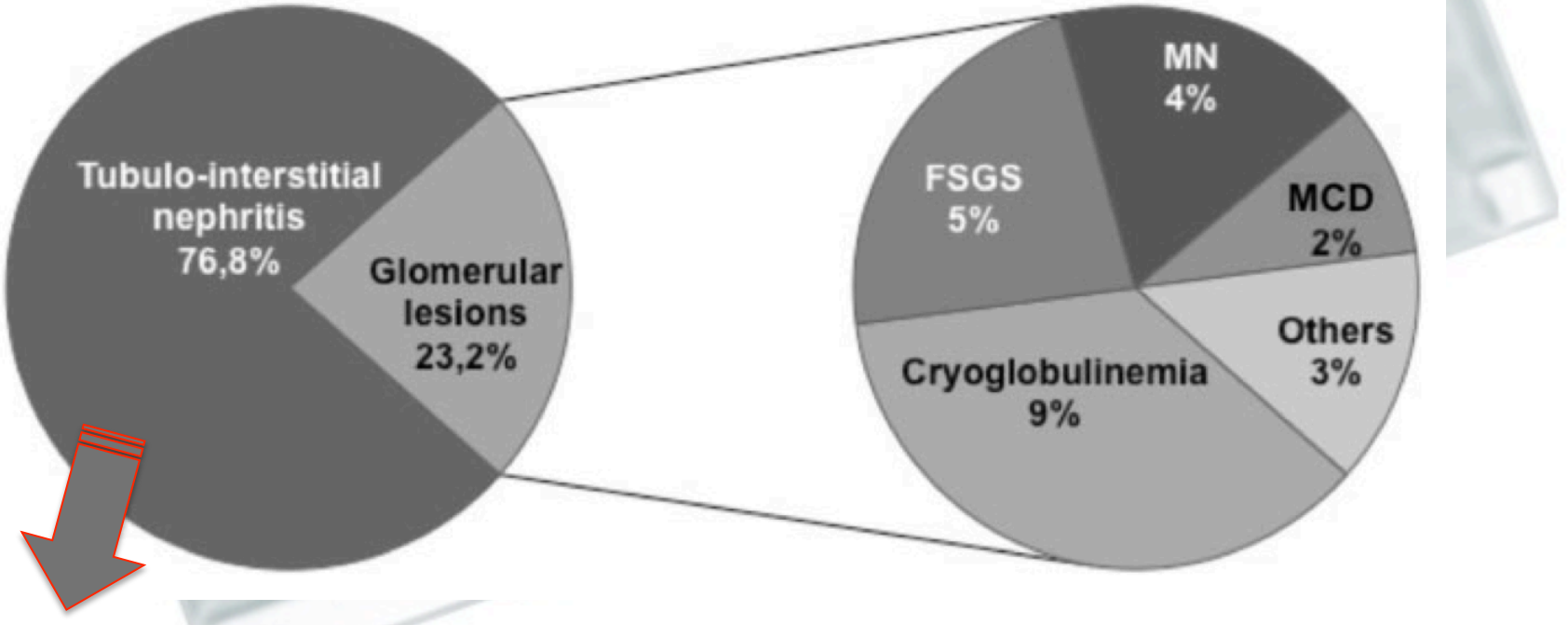
- No DS Sd.Cushing, DM, Insomnio, HTA, DL, UGD, Osteoporosis
- Leucopenia 14.3 vs 0%

A multicentre study of 95 biopsy-proven cases of renal disease in primary Sjogren's Syndrome

Jasiek M Rheumatology 2017

N= 95 SSp (86M), 49→51a (Renal): **IRA 32%, IRC 55%, proteinuria 26%**

FIG. 1 Renal biopsy findings in the 95 patients with pSS



- **<u>81p (85%) recibieron tto IS</u>**: **60**GC, **21** GC+IS mayor (18**RTX**).
- 14p (15%) no recibieron tto IS por cronicidad biopsia.

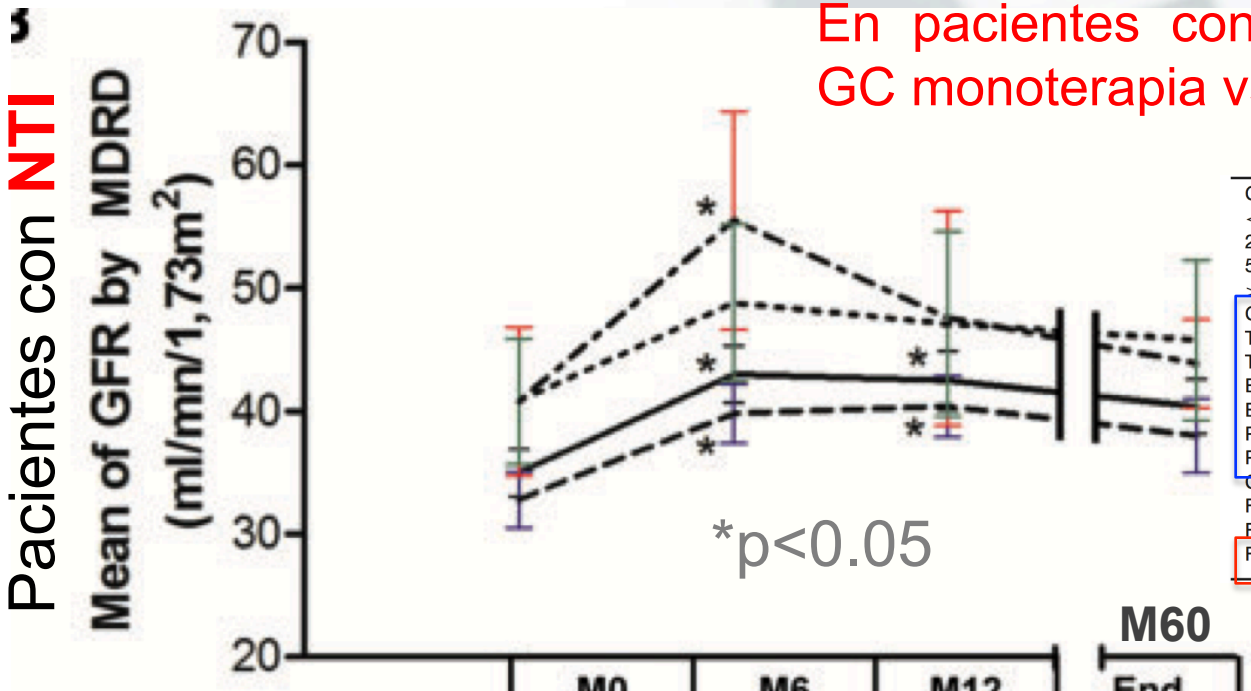
A multicentre study of 95 biopsy-proven cases of renal disease in primary Sjogren's Syndrome

Jasiek M Rheumatology 2017

N= 95 SSp (86M), 49→51a (Renal): **IRA 32%, IRC 55%, proteinuria 26%**

En pacientes con NTI: **No DS** entre GC monoterapia vs GC+ RTX

Pacientes con **NTI**



	M0	M6	M12	End
— All treated	35,0	43,0	42,5	40,4
--- CSs only	32,8	39,8	40,4	38,0
--- CSs + others IS	40,8	55,5	47,6	43,9
---- CSs + RTX	40,8	48,8	47,1	45,8

Cortical area with significant interstitial cellular infiltrat	
<25%	5 (20)
25–50%	6 (24)
50–75%	7 (28)
>75%	7 (28)
Characterization of interstitial cellular infiltrate (*n* = 20)	
T-cell infiltration	20 (100)
T-cell predominant	13 (65)
B-cell infiltration	19 (95)
B-cell predominant	2 (10)
Plasma-cell infiltration	15 (75)
Plasma-cell predominant	5 (25)
Characterization of interstitial fibrosis (*n* = 37)	
Fibrosis, median (IQR), %	27.1 (14–73)
Fibrosis <25%	12 (32.4)
Fibrosis ⩾25%	25 (67.6)

A multicentre study of 95 biopsy-proven cases of renal disease in primary Sjogren's Syndrome

Jasiek M Rheumatology 2017

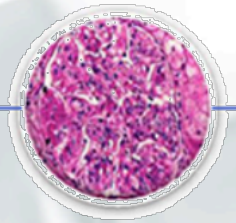
TABLE 4 Baseline characteristics according to the improvement or not of eGFR in patients with **tubulointerstitial nephritis**

Patient characteristics	No eGFR gain or a gain of < 20% (n = 32)	eGFR gain of ⩾ 20% (n = 32)	P-value[a]
Demography and comorbidities			
Gender, female, *n* (%)	30 (94)	30 (94)	0.9
Age at diagnostic, median (IQR), years	46 (31–63)	54 (34–66)	0.4
Age at kidney biopsy, median (IQR), years	51 (35–65)	58 (33–66)	0.5
Hypertension, *n* (%)	3 (9)	11 (34)	0.02[b]
Diabetes, *n* (%)	1 (3)	3 (9)	0.5
pSS characteristics			
ESSDAI, median (IQR)	15 (12–18)	16 (12–20)	0.3
AECG criteria, *n* (%)	28 (88)	26 (81)	0.5
Enlarged criteria, *n* (%)	4 (13)	6 (19)	0.4
(i) Anti-SSA, *n* (%)	31 (97)	23 (72)	0.01
(i) Anti-SSA and -SSB, *n* (%)	25 (78)	17 (53)	0.05
Chisholm score ⩾3, *n* (%)	26 (82)	27 (84)	1
RF positivity, *n* (%)	21 (66)	15 (47)	0.3
Cryoglobulinaemia positivity, *n* (%)	9 (28)	7 (22)	0.5
Serum gammaglobulin, median (IQR), g/l	23 (17–32)	20 (16–38)	0.8
Hypergammaglobulinaemia (>16 *vs* <16 g/l), *n* (%)	26 (81)	25 (78)	0.8
Characteristics of renal involvement			
Delay between renal disease/symptoms of pSS, year, median (IQR)	1.5 (0.5–5.4)	1.0 (0.1–4.3)	0.3
(i) eGFR at inclusion, median (IQR), ml/min/1.73 m^2	40 (33–52)	30 (20–37)	0.002
Isolated electrolyte disturbances, *n* (%)	6 (19)	10 (31)	0.2
Lithiasis, *n* (%)	5 (16)	3 (9)	0.2[b]
Nephrocalcinosis, *n* (%)	4 (13)	1 (3)	0.2[b]
Proteinuria, median (IQR), g/24 h	0.5 (0.3–1.0)	0.5 (0.2–0.8)	0.5
P/C, median (IQR), g/mmol	0.07 (0.03–0.1)	0.05 (0.02–0.1)	0.4
Lymphocyte infiltration, *n* (%)	32 (100)	26 (81)	0.2
Plasmocyte infiltration, *n* (%)	23 (72)	16 (50)	0.5
Fibrosis >25% *vs* ⩽25%, *n* (%)	8/13 (62)	13/18 (72)	0.9
Degree of cellular infiltration<50% *vs* ⩾50%, *n* (%)	9/21 (43)	12/21 (57)	0.08[b]

Table V. Characteristics of clinical studies with TIN alone pSS patients treated with immunosuppressive agents.

Group (ref)	Treated TIN alone patients	Untreated TIN alone patients	Outcome	Confounders
Maripuri *et al*. (6) 2009	• 15 patients **NTI (Bx)** • mainly prednisone, median initial dose 40mg/d (range 30-60mg/d) for median duration of 30w	0 patients	>20% eGFR gain responders: 9	No information
Kidder *et al*. (5) 2015	• 7 patients **NTI (Bx)** • mainly prednisone (no information for dose or duration)	4 patients	• Treated patients (>20eGFR gain) º 4 patients: no º 3 patients: yes • Untreated patients (>20 eGFR gain) º 3 patients: yes º 1 patient: RRT	No information
Evans *et al*. (26) 2016	• 11 patients **NTI (Bx)** • mainly prednisone, median initial dose 10mg/d (range 5-20) weaned over 3-6 months + MMF median dose 1000mg/d for median duration 24 months	1 patient	Median eGFR change 10ml/min/1.73m² (at follow-up) • Pre=32ml/min/1.73m² • Post=42ml/min/1.73m²	No information
Jasiek *et al*. (23) 2017	• 64 patients **NTI (Bx)** • prednizone median initial dose 55mg/d (range 5-80mg/d) for variable duration but at least for 6 months plus rituximab, AZA or MMF	8 patients	• Mean GRF change 7.5ml/min/1.73m² • pre=35, post=42.5 (at 12 month follow-up)	No information
Shen *et al*. (27) 2017	• 56 patients **NTI (30Bx) ó P.Tubular/ATR** • prednisone mean initial dose 25.5mg/d for more than 3 months	0 patients	Mean GFR change: 2.72±19.11 ml/min/1.73m² (at 12 month follow-up) Pre=64.86±30.45 ml/min/1.73m²	ACEi, ARB
Goules *et al*. 2019	• 8 patients • Prednizone initial dose 20-60mg/d for at least 2 months plus MMF, AZA, MTX or anti-TNF (1 case) **5 NTI (Bx), 2 hipoK severa, 1 Hematuria/litiasis**	6 patients	• Treated patients (>20eGFR gain) º 6 patients: no º 2 patients: yes • Untreated patients º 2 patients: NRF (after years) º 4 patients: RRT (after years)	ACEi, ARB, NSAIDs, diuretics, HTN, DM

EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies



RENAL INVOLVEMENT

Tubular involvement

Glomerulonephritis *Rule out ANCA, SLE*

Mild ESSDAI

1st-line	Symptomatic*	4

ATR sin IR, Glomerular prot **0.5-1**gr/d sed normal, eGFR>60ml/min

No response

Moderate ESSDAI

1st-line	GC (0.5)	4
2nd-line	Oral ID**	4

ATR con IR eGFR<60ml/min, Glomerular PRU **1-1.5**gr/d sed normal, GN no MP (bx), NTI linfoide importante (bx)

No response

High ESSDAI

1st-line	GC (0.5-1)	4
2nd-line	RTX*** or CyC	4
Rescue	Pex****	4

Glomerular **PRU>1.5**gr/d ó **sedimento activo** ó **IR** eGFR<60ml/min o **GNMP/ crioglobulinemia renal**.

*Symptomatic: correction of the metabolic acidosis/K levels

**no head-to-head comparisons (consider Aza, CyA, MMF)

***Cryo vasculitis

****Life-threatening cryo vasculitis

Manuel Ramos-Casals , Pilar Brito-Zerón et al On behalf of the EULAR-Sjögren Syndrome Task Force Group. Ann Rheum 2019, Octubre

Conclusiones: afectación renal en SSp

- Rara: **40%** latente, **3-5%** manifiesta
- Suele ser **LATENTE** → orina en todos (**Ph, B2 microglobulina, Osmolaridad urinaria**…)

Box 4 | **Recommended biologic screening during pSS**

Once a year if pSS with systemic involvement

- Serum dosage: creatinine, potassium, bicarbonate, chloride
- Urinary testing: morning urinary dipstick with pH, urine osmolality and glycosuria; protein to creatinine ratio

Every 6 months if anomalies are detected

- Serum dosage: creatinine, potassium, bicarbonate, chloride, phosphate, uric acid
- Urinary testing: morning urinary dipstick with pH, urine osmolality, and glycosuria; 24 h urinary volume, proteinuria, creatininuria, calciuria, citraturia, urinary sediment and culture
- Perform renal ultrasound
- Discuss renal biopsy

Conclusiones: afectación renal en SSp

- Rara: **40%** latente, **3-5%** manifiesta
- Suele ser **LATENTE** → orina en todos (**Ph, B2 microglobulina, Osmolaridad urinaria**…)
- La **NTI** es la mas frecuente (infilt. linfoplasmocitaria):
  - ↳ Respuesta a Esteroides (IS=ahorradores esteroides)
- La **GNMP** (crioglobulinas), C4 → Screening **Linfoma**

*Amplio abanico de posibilidades y **no muy buena correlación clínico-patológica**: NTI, GN MP, GN MB, CM, GN Crioglobulinémica, vasculitis necrotizante, GnIgA, nefrocalcinosis, litiasis, sarcoidosis, linfoma*

- **Biopsia Renal** si Insuficiencia renal y/o proteinuria (Alb)
- **Tratamiento** dirigido a la lesión: K/Bic, GC, IS mayores
- Estrecha colaboración entre **MI-Nefrología**

ESTUDIO MULTICÉNTRICO DE LA ENFERMEDAD RENAL TUBULOINTERSTICIAL Y GLOMERULAR EN PACIENTES CON SÍNDROME DE SJÖGREN PRIMARIO

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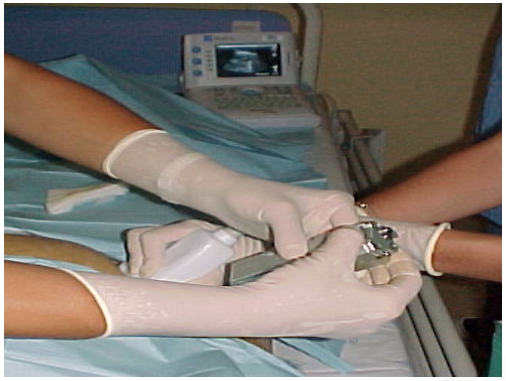


Biopsia renal en SSp

- Multi/Pluri**variedad** de afectación renal en el SSp.
- **DISOCIACIÓN CLÍNICO-PATOLÓGICA** renal
- DD y coexistencia **NTIA** vs **GN** (+/- Crioglobulinemia renal)
- Tratamiento: **Corticoides,** Rituximab, MMF, Ciclofosfamida…

- **Insuficiencia Renal** (↓FG)
- **Proteinuria +/- Sedimento activo**

→ Descartando AINEs, Nefrocalcinosis, Litiasis, ITUs…

Table 2 | **Renal biopsy findings in primary Sjögren syndrome**

Renal biopsy finding	Study	Diagnostic criteria	Positive biopsies/ total biopsies (%)
Tubulointerstitial nephritis	Bossini *et al.* (2001)[3]	European–1993*	6/9 (66.0)
	Ren *et al.* (2008)[22]	AECG	33/41 (80.5)
	Maripuri *et al.* (2009)[21]	AECG	17/24 (71.0)
	Lin *et al.* (2010)[8]	AECG	21/61 (33.0)
	Goules *et al.* (2013)[25]	AECG	12/33 (33.0)
MPGN secondary to cryoglobulinaemia			1/9 (11.0)
			2/41 (4.9)
			2/24, (8.0)
			10/33 (30.0)
Membranous nephropathy			1/9 (11.0%)
			1/41 (2.4%)
			1/24 (4.0%)
			10‡/64 (15.6)
			2/33 (6.0)
IgA nephropathy			1/9 (11.0)
			3/41 (7.3)
			7/33 (21.0)
Focal segmental glomerulosclerosis			2/41 (4.9)
			2/24 (8.0)
			1/64 (1.5)
			1/33 (3.0)
Minimal change disease			1/24 (4.0)
Unspecified proliferative glomerulonephritis	Lin *et al.* (2010)[8]	AECG	25/64 (39.0)
	Goules *et al.* (2013)[25]	AECG	1/33 (3.0)
Crescentic glomerulonephritis	Dussol *et al.* (1994)[66]	European–1993*	Case report
	Kamachi *et al.* (1999)[67]	European–1993*	Case report
	Tatsumi *et al.* (2000)[68]	European–1993*	Case report
	Wang *et al.* (2011)[69]	AECG and enlarged AECG	Case report
	Guellec *et al.* (2015)[70]	AECG (5/7 patients)	N/A
Global glomerulosclerosis	Maripuri *et al.* (2009)[21]	AECG and enlarged AECG	1/24 (4.0)

- NTI 43-80% de las Bx
- GNMP 5-30%
- GNMB 3-15%
- NIgA 7-21%
- GEFS 1.5-8%
- GNCM 4%
- Extracapilares ocasional

Francois H Nat Rev Nephrology 2015

Síndrome de Sjogren y nefropatía mixta. La importancia de la precocidad en la biopsia renal

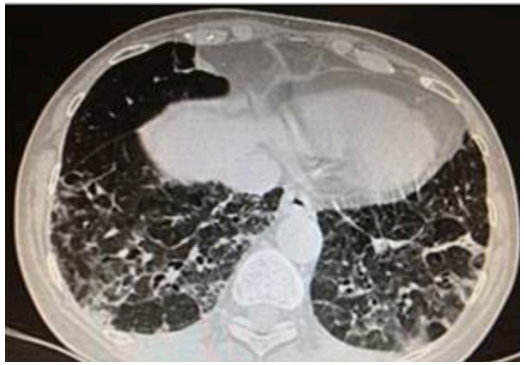
Mujer 76 años

AP: HTA bien controlada con 2 fármacos y SSp con afectación glandular (biopsia) y extraglandular (fibrosis pulmonar, púrpura cutánea corticodependiente, raynaud)

Tratamiento: azatioprina, prednisona 5 mg/día, bifosfonato, calcio-vitamina D, pentoxifilina, acetilcisteína, perindopril 4 mg y amlodipino 5 mg.

Ingreso julio de 2013 por brote purpúrico en miembros inferiores, debilidad, fiebre de 37,8°C, tos irritativa, náuseas y vómitos biliosos, junto con pérdida ponderal de hasta 10 kg de peso en 2 meses.

EF: púrpura cutánea y la hipoventilación bibasal, atribuida a su fibrosis pulmonar.



NEFROLOGIA 2016;36(4):444–463

Síndrome de Sjogren y nefropatía mixta. La importancia de la precocidad en la biopsia renal

Insuficiencia renal aguda y sedimento activo leves (creat 1.07, FG 56, 20H/C – 56% dismorfias), Proteinuria 0.38gr/d

Autoinmunidad habitual positiva (ANA+,Ro+,La+, hipocomplementemia **C4 1** mg/dl, IgM y FR muy elevados).

Además de, en la actualidad, hipocomplementemia **C3 66** mg/dl, descenso de IgG 600 mg/dl (previamente normal) y **crioglobulinas positivas** **(dudosa monoclonalidad)**.

Serología para hepatitis C,B y para VIH, negativa. ANCA negativos.

NEFROLOGIA 2016;**36(4)**:444–463

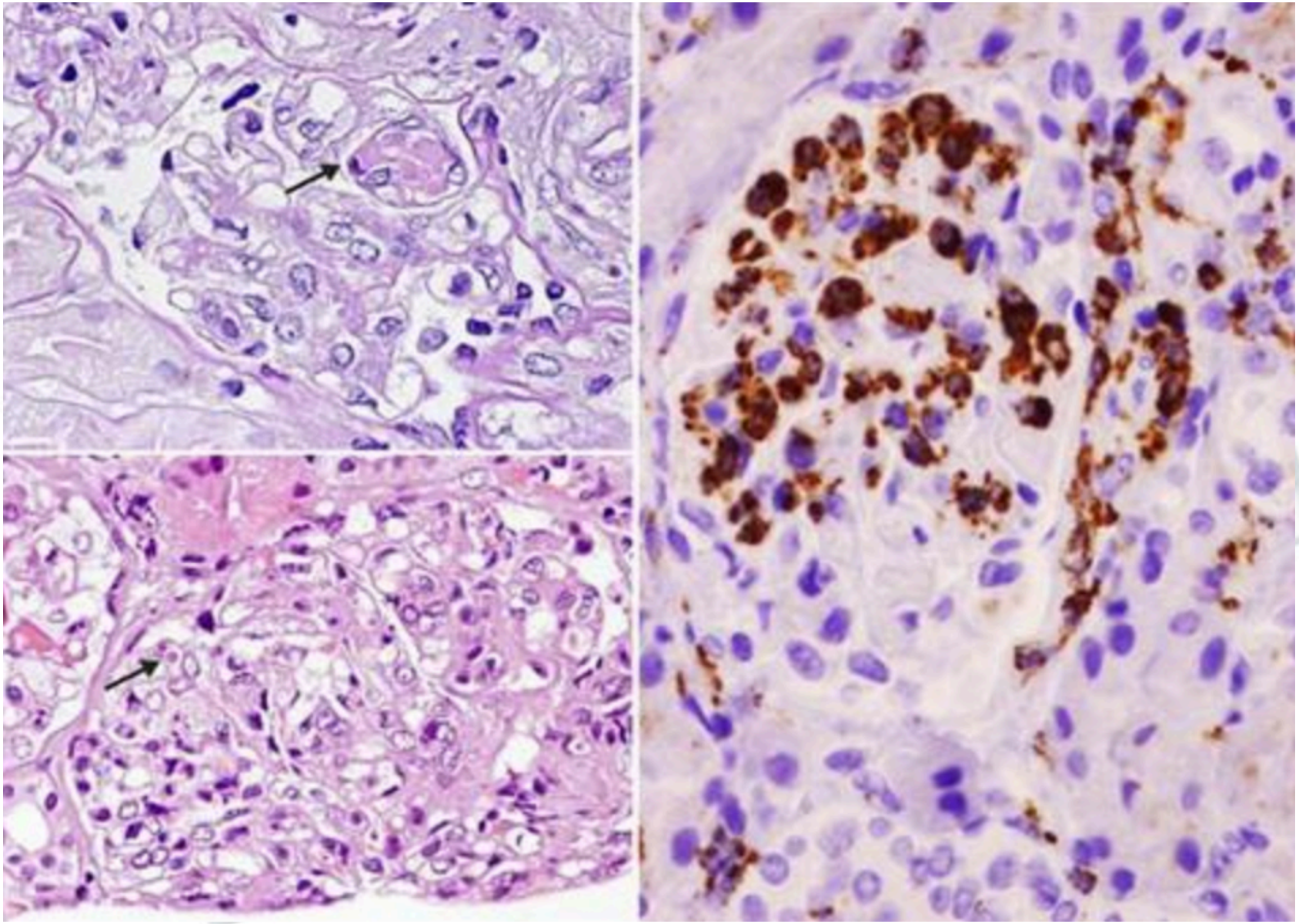


Figura 2 – Biopsia renal. Glomérulos con proliferación mesangial y endocapilar en los que se observan ocasionales, pseudotrombos hialinos de distinto tamano˜ (flechas). A) PAS 60x. B) Hematoxilina eosina 40x. C) Presencia de numerosos macrófagos intraglomerulares. Inmunohistoquímica para CD 68 40x.