VII. Aydın Romatoloji Günleri

Ana Tema: Sjögren Sendromu

14-16 Ekim 2022

Korumar Ephesus Resort Otel

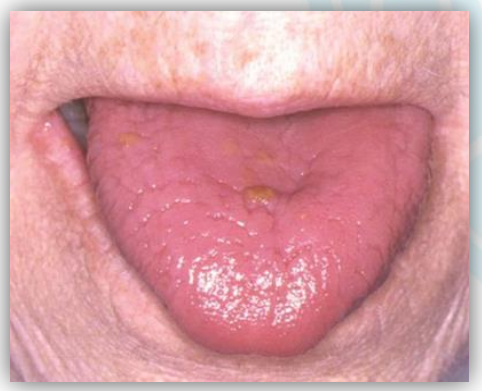
Sjögren Sendromunda Böbrek Tutulumu

Dr. İsmail SARI, MSc

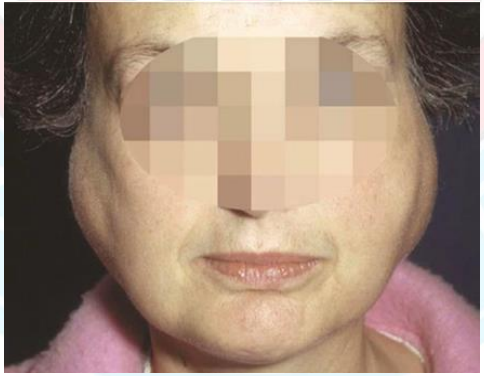
Otoimmün hastalık

Mukozada sikka semptomları

Sistemik bulgular (ekstraglandüler tutulum)



Histolojide tutulan bezde fokal lenfositik infiltrasyon



Sitopeniler

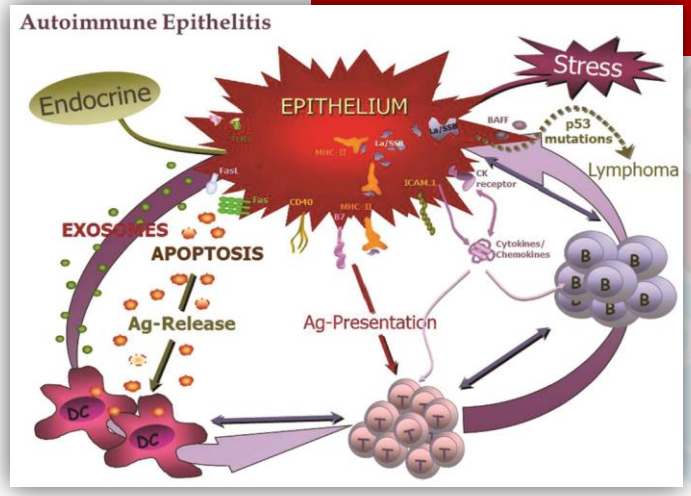
Akut faz yanıtı

Otoantikorlar
Anti-SSA (en spesifik)

Kryoglobulin ve hipokomplementemi (prognostik)

Sjögren Sendromu

Primer

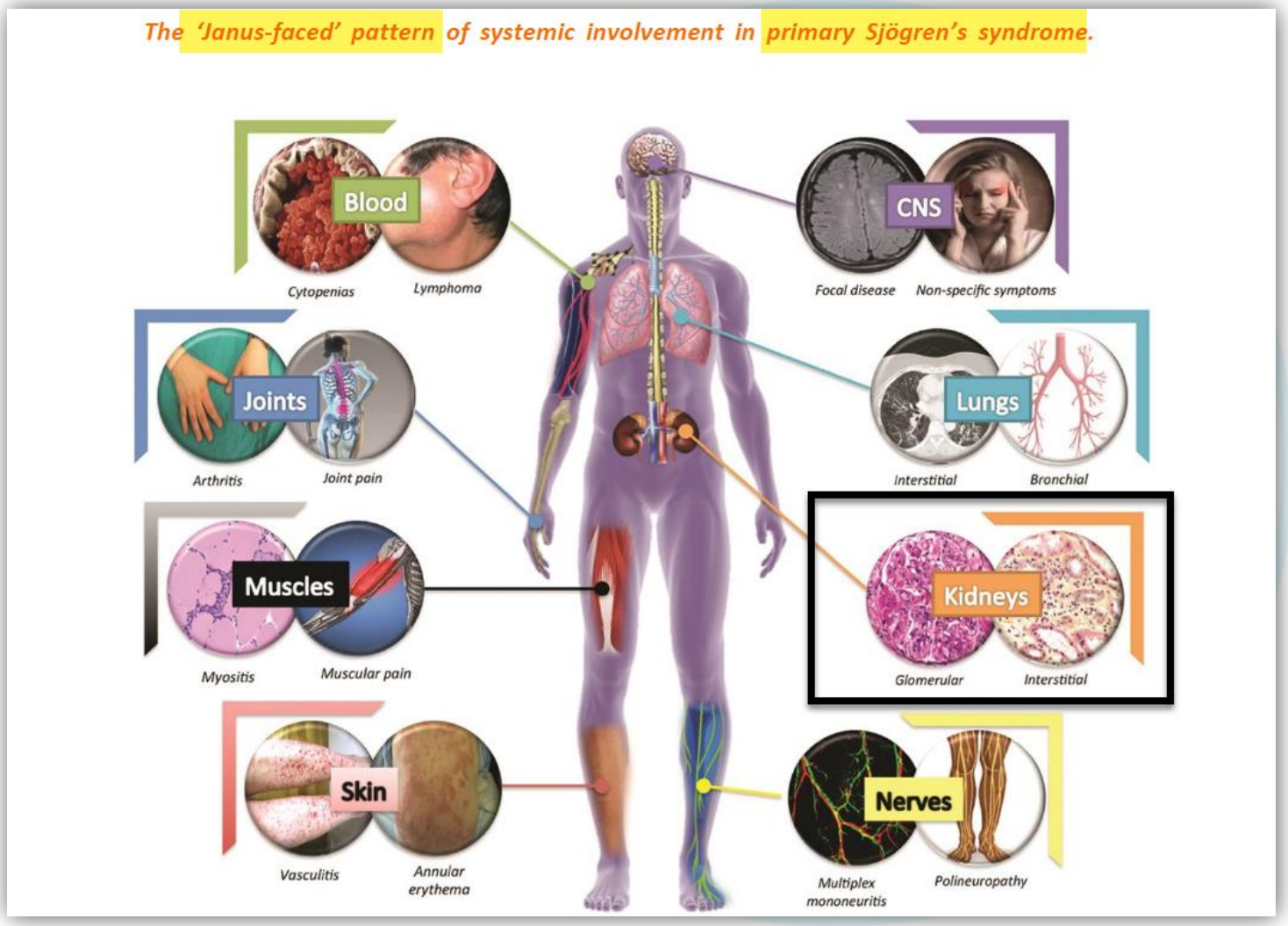


Sekonder (en sık RA, SLE ve Scl)

Secondary SS

a. Systemic autoimmune diseases
- Systemic lupus erythematosus.
- Systemic sclerosis.
- Rheumatoid arthritis.
- Still's disease.
- Sarcoidosis.
- Inflammatory myopathies.

b. Organ-specific autoimmune diseases/infections
- Primary biliary cirrhosis.
- Autoimmune hepatitis.
- Autoimmune thyroiditis.
- Coeliac disease.
- Multiple sclerosis.
- Diabetes mellitus.
- Chronic viral infections.
- Chronic hepatitis C virus infection.
- HTLV-I infection (Asian countries).
- HIV infection.



Sekonder

İlaç

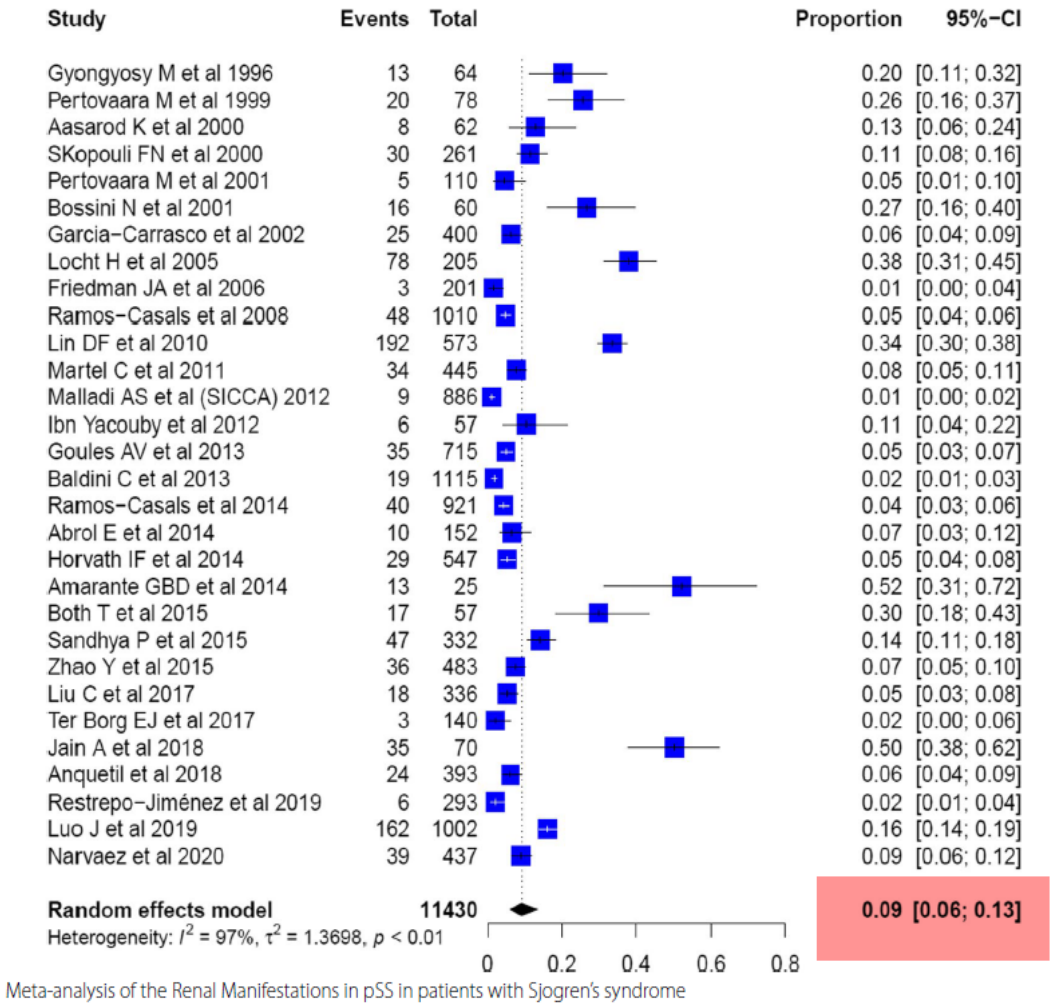
Enfeksiyon

Altta yatan hastalık (SLE)

Organ	Manifestation
Skin	Purpura (10–15%) often related to cryoglobulinaemia Annular erythema (photosensitive erythematous lesions with indurated borders; 5–10%)
Joints	Non-erosive symmetrical arthritis (15–30%)
Lungs	Chronic obstructive lung disease (10%) Bronchiectasis (8%) Interstitial lung disease (5%)
Cardiovascular	Raynaud's phenomenon (18–37%) Pericarditis (<5%) Symptoms of autonomic dysfunction
Liver	Primary biliary cirrhosis (3–8%) Autoimmune hepatitis (<5%)
Pancreas	Recurrent pancreatitis (<5%)
Nephro-urological	Renal tubular acidosis (11%) Glomerulonephritis (<5%) Interstitial cystitis (<5%) Nephrolithiasis (<5%)
Peripheral nerves	Mixed polyneuropathy (5–10%) Pure sensory neuronopathy (5%) Mononeuritis multiplex (5%) Small-fibre neuropathy* (<5%) Myoclonus
Central nervous system	White matter lesions (MS-like disease) (<5%) Cranial nerve involvement (V, VIII and VII) (7%) Myelitis (<5%)
Thyroid	Autoimmune thyroiditis (14–33%)
Haematological	Autoimmune haemolytic anaemia (<5%) Severe thrombocytopenia <10 000/mm^3 (<5%) B cell lymphoma (5–10%)

Sjögren sendromu(SS)' nun klinik belirtileri sadece ekzokrin bez tutulumu ile sınırlı olmayıp, hastaların ***yaklaşık %15'inde*** ekstra-glandüler tutulumlar görülür

Ramos-Casals et al, BMJ 2012b;344:e3821



Meta-analysis of the Renal Manifestations in pSS in patients with Sjogren's syndrome

- Renal tutulum sıklığı %1-33 bildirilmiştir
  - Genel kabul primer SS hastalarının yaklaşık %5'inde böbrek tutulumu olduğu yönünde
    - Çalışmalar arasındaki yöntemsel farklılıklar

%9

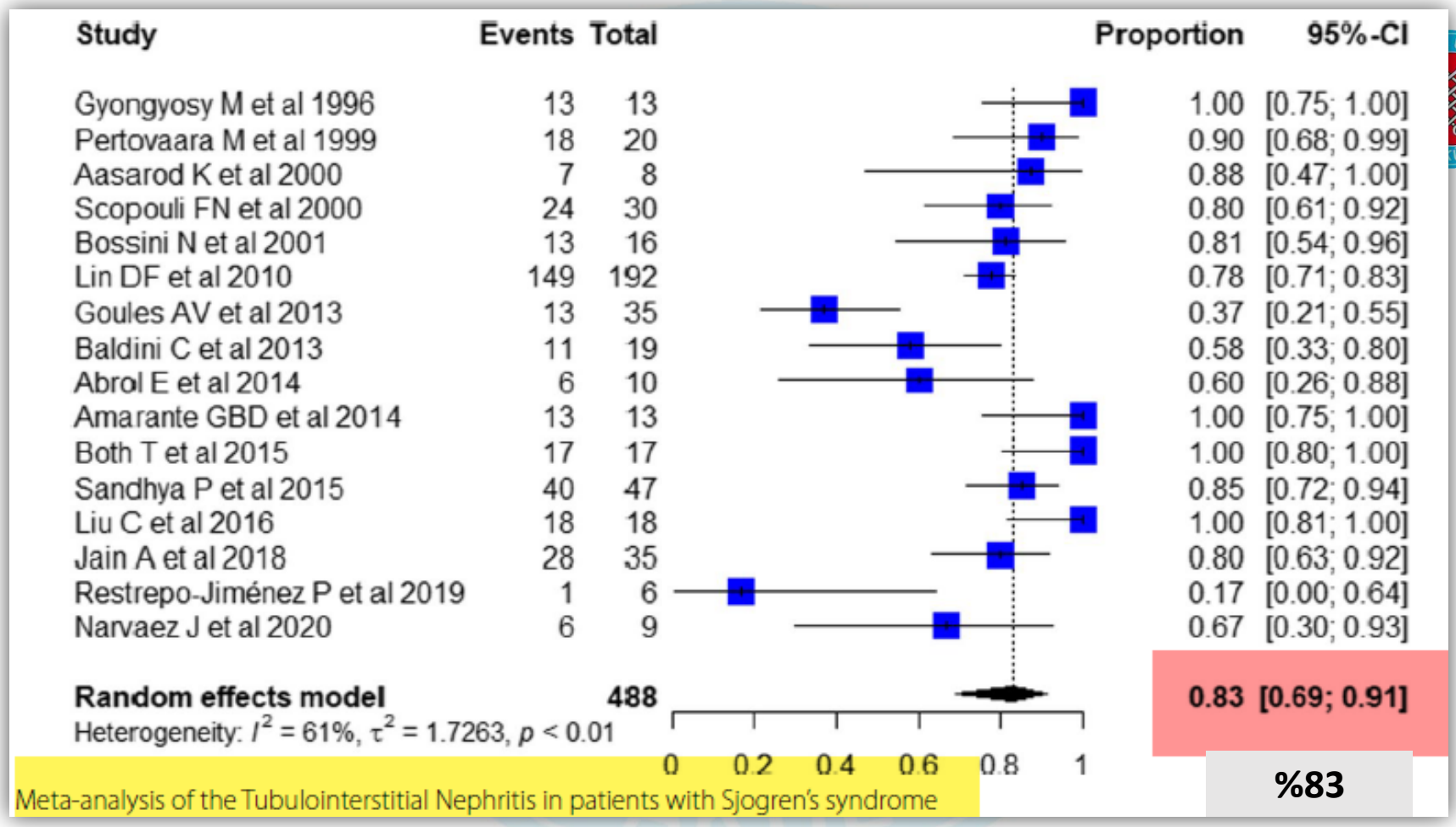
Trevisani et al. Advances in Rheumatology (2022) 62:18
François H ve ark. Nat Rev Nephrol. 2016;12(2):82-93.
Ramos-Casals M ve ark. Rheumatology (Oxford). 2015;54(12):2230-8
Yang HX ve ark. Int J Rheum Dis. 2018 Jan;21(1):223-229

Primer Sjögren sendromunda sık görülen renal tutulum paternleri

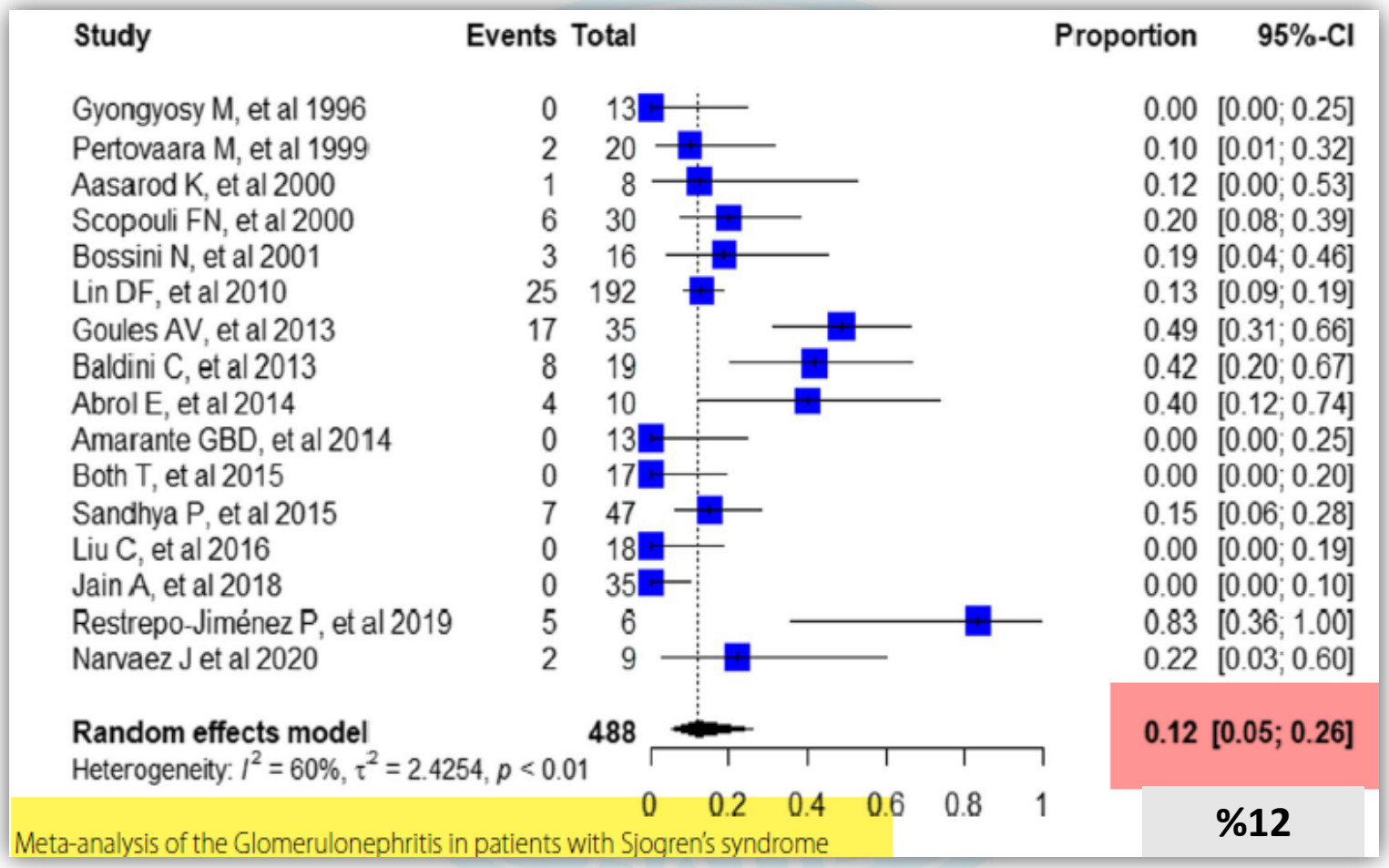
- İzole elektrolit bozuklukları
- Distal renal tübüler asidoz
- Nefrojenik diabetes insipidus
- Fanconi sendromu
- Gitelman sendromu
- Bartter sendromu
- Akut tübülointerstisyel nefrit (TIN)
- Kronik TIN
- Glomerüler hastalık (En sık MPGN)

Yaklaşık %70 hastada renal biyopsi pSS tanısı almadan önce yapılmış!!

Kidder D ve ark. Nephrol Dial Transplant. 2015;30:1363-9
Ramos-Casals M ve ark. Rheumatology (Oxford). 2015;54(12):2230-8
Yang HX ve ark. Int J Rheum Dis. 2018 Jan;21(1):223-229



Trevisani et al. Advances in Rheumatology (2022) 62:18



Trevisani et al. Advances in Rheumatology (2022) 62:18

Tubulointerstisyel nefrit

- En sık görülen tutulum
- Akut veya Kronik
- interstisyumda lenfositik infiltrasyon
  - İnfiltrat çoğunlukla CD4+ T lenfositleri
  - CD8+ T lenfosit ve plazma hücre infiltrasyonu da görülebilir
  - Vakaların yaklaşık %10'unda B hücreler de saptanmaktadır
  - Histopatolojik incelemede ***granülom beklenmez***
    - Granülom varlığı, sarkoidoz ve tübülointerstisyel nefrit ve üveit **(TINU)** sendromu açısından şüphelendirmelidir
  - ***Kronikte tubuler atrofi ve fibrozis***
    - ***Glomerüller genellikle normal***

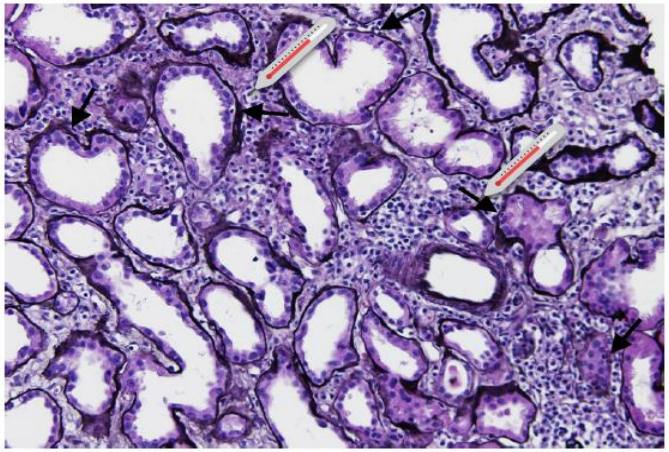


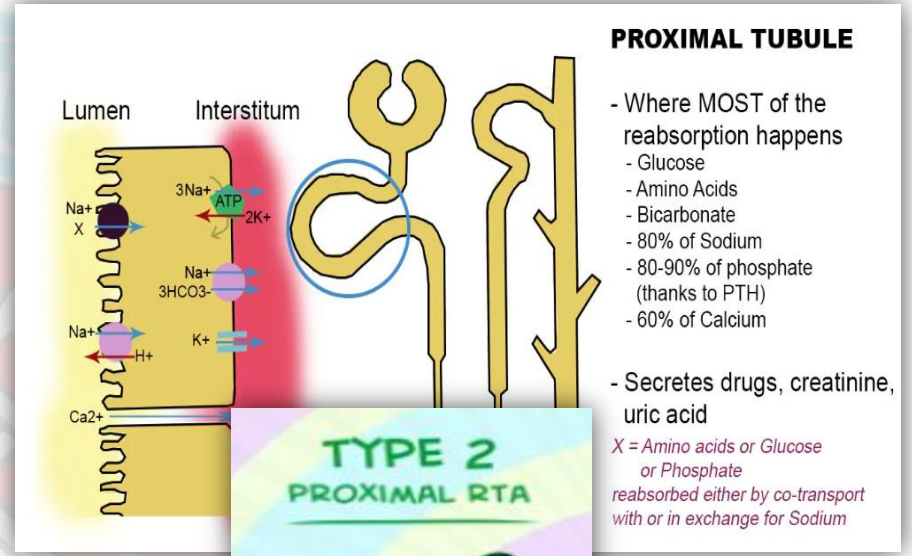
Figure Sjögren syndrome with interstitial lymphoplasmacytic infiltrate with tubulitis (arrows) involving areas of interstitial fibrosis and tubular atrophy (Jones silver stain).

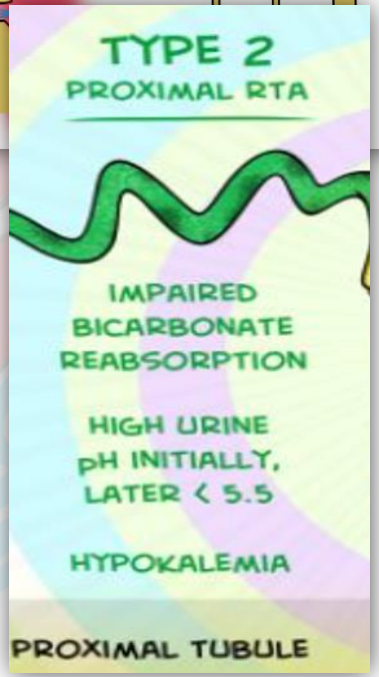
Goules A ve ark. Medicine (Baltimore). 2000 Jul;79(4):241-9.
Bossini N ve ark. Nephrol Dial Transplant. 2001;16(12):2328-36.
Ren H ve ark. J Rheumatol. 2008;35(2):278-84.
Matsumura R ve ark. 1988;30(6):335-40.

- Klinik asemptomatik-semptomatik
- Tutulum yerine göre çeşitli klinik ve laboratuvar
  - Plazma kreatinin düzeyinde hafif yükselme
  - İdrarı konsantre etme yeteneğinde bozukluk
  - İdrar PH'sında yükselme
  - Hipokloremik metabolik asidoz
  - Tubuler proteinüri
  - Poliüri, nokturi, polidipsi
  - Nefrolitiazis
  - Hipokalemi

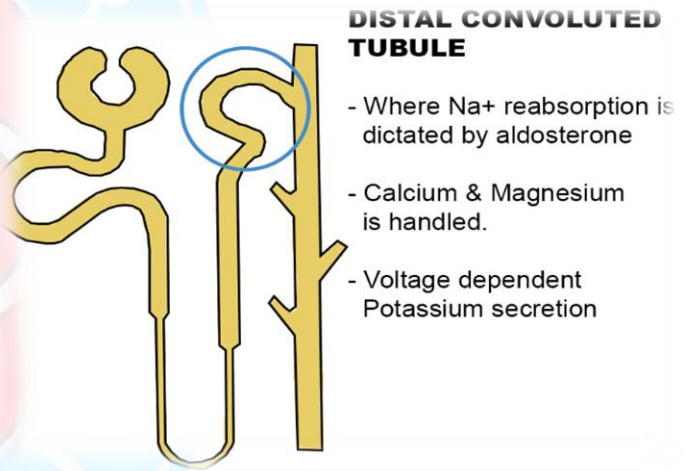
Location	Functions	Reabsorbed (aside from water)	Secretes	Main Transporters	Diuretic
Proximal Tubule	• Major site of reabsorption overall • The only site of glucose, AA & PO4 reabsorption • Regulates pH of filtrate	Na K PO4 Ca Mg AA Glucose Bicarbonate	Drugs Creatinine Uric Acid H+	Na/H+ Reabsorption occurs either in co-transport with or exchange for Na	Carbonic anhydrase
Loop of Henle	• Some electrolyte reabsorption • Creates a concentration gradient for water reabsorption using a counter-current multiplier •	Na K Cl Ca Mg	Recycles K to provide a +ve luminal charge that encourages Ca/Mg uptake between cells	NKCC2 Aquaporins	Loop diuretic
Distal Convoluted Tubule	• Further electrolyte control • Main site that can control Ca, Mg using dedicated channels and active transporters	Na Ca Mg	K	NCC	Thiazide
Collecting Duct	• Salt and water reabsorption under influence of aldosterone and ADH • Regulates pH of filtrate • Potassium & hydrogen secretion	Na Bicarbonate	K, H+	ENaC (regulated by aldosterone) Aquaporins	K sparing

- Proksimal RTA ve Fanconi sendromu
  - Tip 2 RTA
  - ***Distale göre daha az görülür***
  - Proksimal tubul glomerüler filtrasyonun emiliminin çoğundan sorumludur
  - ***Normal anyon açıklı asidoz, hipofosfatemi, hipoürisemi ile karakterizedir***
  - ***Normoglisemik glikozüri proksimal tübüler asidoz için spesifik bir bulgudur***
  - Önce daha sık görülen diğer nedenler (***Wilson hastalığı, myelom, ilaçlar, toksisite*** gibi) dışlanmalıdır

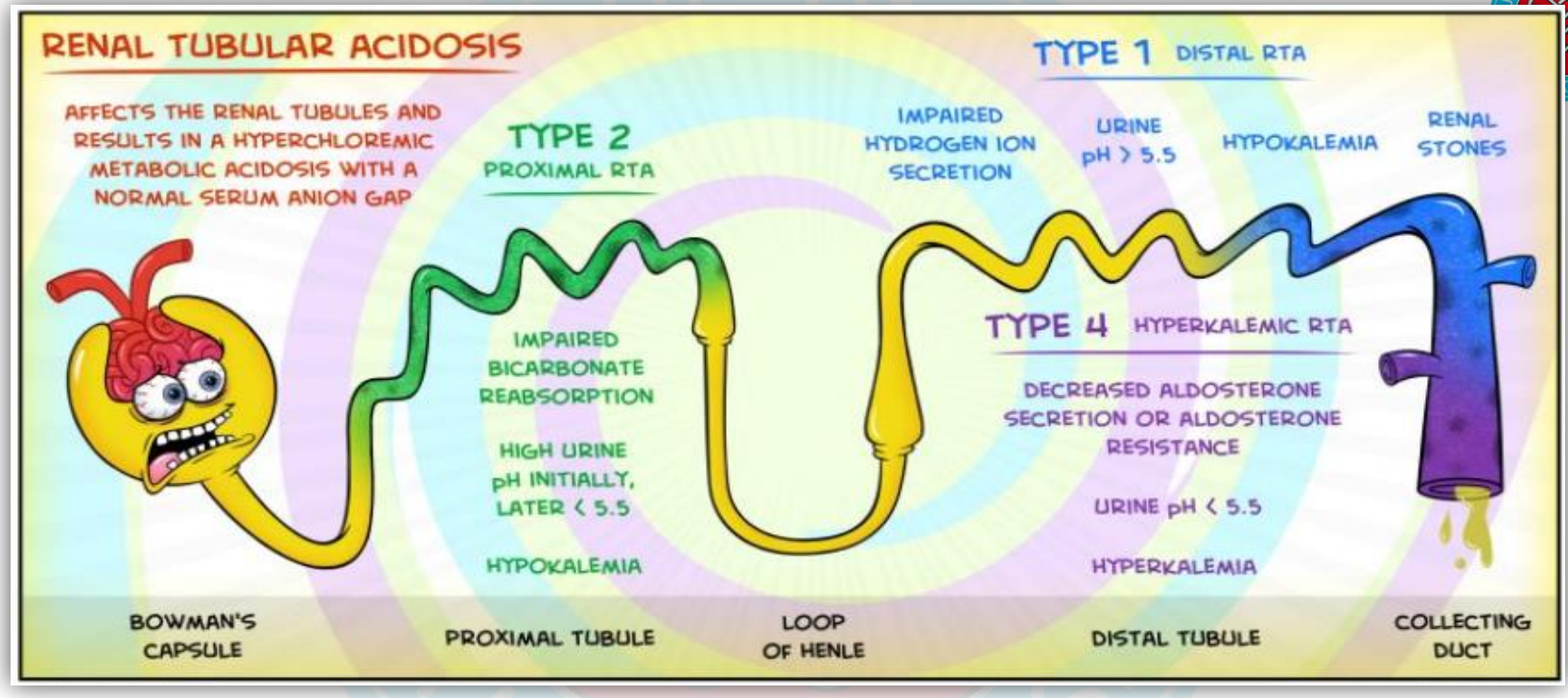




- Distal RTA
  - SS hastalarının ***yaklaşık %25'inde distal asidifikasyon*** kusuru gelişir.
  - Mekanizma?
    - Toplayıcı tubullerdeki ***alfa interkale hücrelerde H*** salınımından sorumlu olan H-ATP az pompasında tam kayıp veya ***karbonik anhidraza*** karşı otoantikor gelişimi
  - Distal nefrondaki ***yetersiz hidrojen atılımı***
  - ***Normal anyon açıklı metabolik asidoz ve idrar pH > 5.5 ile karakterizedir***
  - ***Asidozun neden olduğu idrarda potasyum kaybı hipokalemi ile sonuçlanır***
  - ***Hiperkloremi, hiperkalsiüri ve hipositratüri görülebilir***
    - ***Nefrolityazis (hiperkalsüri ve hipositratüri)***



- Gitelman (daha sık)
  - Tuz kaybettiren tübülopati
  - Klinik özellikleri ***kronik tiazid*** kullanımı ile benzerlik gösterir
    - ***Alkaloz, hipokalemi (artmış idrar potasyum atılımı , >20mmol/l), hipomagnezemi , hipokalsiüri, hipermagnezüri ve sekonder hiperaldesteronizm***
- Bartter
  - Primer SS'de Gitelman sendromuna göre daha nadirdir
  - Henle kulpu çıkan kalın kolunda sodyum klorür emiliminin azalması sonucu gelişir.
  - ***Loop diüretik*** kullanımı ile uyumlu klinik bulgular saptanır.
    - Alkaloz, hipokalemi, sekonder hiperaldosteronizm ve hipomagnezemi
    - Gitelman sendromundan farklı olarak ***idrar kalsiyum atılımı*** normal veya yüksektir



https://www.paediatricfoam.com/2020/08/tubulopathies4/

Hypokalemic Paralysis due to Primary Sjögren Syndrome: Case Report and Review of the Literature

Case Reports in Rheumatology
Volume 2017, Article ID 7509238, 7 pages

A. Garza-Alpirez, A. C. Arana-Guajardo, J. A. Esquivel-Valerio, M. A. Villarreal-Alarcón, and D. A. Galarza-Delgado

- Hipokalemi-Renal tübüler asidoz olmaksızın
  - Hipokalemi, renal hastalığın olduğu primer SS'de yaygın bir bulgudur ve hastaların yaklaşık %30-47'sinde görülür.
  - ***SS'de metabolik asidoz ve idrar asidifikasyon kusuru olmadan da hipokalemi gelişebilir.***
  - Hipokalemiye neden olan birincil kusurun sodyum kaybı olduğu düşünülmektedir.
    - ***Toplayıcı tübüllerdeki azalan sodyum düzeylerinin potasyum sekresyonunda artışa*** neden olması ve volüm kaybı sonucu aldosteron salgılanması.
      - Bu klinik **özellikler Gitelman sendromunu** taklit eder
  - ***Hipokalemisi olan ve renal biyopsi yapılan primer SS hastalarının hepsinde TIN saptandığı bildirilmiştir***.

- Nefrojenik diabetes inspidus (NDİ)
  - SS'de bozulmuş tübüler fonksiyonun başka bir yansıması
  - Tübüler (kollektör) düzeyde vazopressine (ADH) yanıtsızlık
  - İdrar konsantrasyonu bozulur.
  - Poliüri ve polidipsi
  - ***Kronik lityum kullanımı ve hiperkalsemi dışlandıktan sonra NDİ etyolojisi araştırılan hastalarda SS açısından değerlendirme yapılmalıdır***

Glomerüler hastalık

- TIN’ e göre daha az ve primer SS'nin geç komplikasyonu
  - Membranoproliferatif glomerülonefrit (MPGN) ve membranöz nefropati en sık görülen glomerüler patolojilerdir.
  - Minimal lezyon hastalığı, immünoglobulin A nefropatisi, fokal segmental glomerüloskleroz ve antinötrofil sitoplazmik antikor ilişkili vaskülit
- Klinik
  - Nefrotik sendrom, nefritik sendrom ya da hızlı ilerleyen GN olarak seyredebilir.
- Patogenez?
  - İmmun kompleksler ve kriyoglobulinler (Tip II)
- ***Düşük C3-C4 ve kriyoglobulinemi varlığı tubuler tutulumdan ziyade glomerül tutulumu öngördürebilir***

- MPGN
  - Biyopsi ile doğrulanan renal hastalığın %5-30 arasında değişen sıklıkta kriyoglobulin ilişkili MPGN olduğu bilinmektedir.
  - ***Hipertansiyon, proteinüri ve hematüri*** MPGN seyrinde sık gelişen bulgulardır.
  - ***Nefritik sendroma*** bağlı akut böbrek yetmezliği ve hızlı ilerleyen GN görülebilir.
  - Kriyoglobulinemi aracılı MPGN'de ***sistemik vaskülite*** bağlı çoklu organ yetmezliği görülebilir
- Membranöz nefropati
  - Böbrek biyopsisi yapılan primer SS hastalarının yaklaşık % 10'u
  - ***SLE tanısı dışlanmalıdır***.
  - Membranöz nefropati, diğer nedenlere bağlı olarak da oldukça sık görülür.
    - ***primer SS ve membranöz nefropati ilişkisi net değildir***

Variables	Cryoglobulins (+)[a]		Cryoglobulins (-)[a]	
	CV (+) Group 1 (n = 21)	CV (-) Group 2 (n = 44)	Group 3 (n = 450)	P-value[b]
ESSDAI domains (activity), n (%)				
Constitutional domain	16 (76.2)	12 (27.3)	131 (29.1)	<0.001
Lymphadenopathy domain	13 (61.9)	17 (38.6)	72 (16)	<0.001
Glandular domain	13 (61.9)	19 (43.2)	130 (28.9)	0.002
Articular domain	16 (76.2)	27 (61.4)	207 (46)	0.005
Cutaneous domain	21 (100)	13 (29.5)	93 (20.7)	<0.001
Pulmonary domain	5 (23.8)	10 (22.7)	48 (10.7)	0.016
Renal domain	4 (19)	3 (6.8)	11 (2.4)	0.002
Muscular domain	0 (0)	0 (0)	7 (1.6)	1.000
Peripheral nervous system domain	15 (71.4)	6 (13.6)	48 (10.7)	<0.001
CNS domain	1 (4.8)	2 (4.5)	20 (4.4)	1.000
Haematological domain	18 (85.7)	33 (75)	293 (65.1)	0.076
Biological domain	21 (100)	44 (100)	246 (54.7)	<0.001

- Kryoglobulineminin HCV' den sonra en sık görülme nedeni SjS
- Böbrekteki yansıması genellikle MPGN

Retamoza ve ark. Rheumatology 2016;55:14431451
Kidder D ve ark. Nephrol Dial Transplant. 2015;30:1363-9.

Secondary Renal Amyloidosis due to Long-Standing Tubulointerstitial Nephritis in a Patient With Sjögren Syndrome

Vanessa Ooms, MD, Marc Decupere, MD, Evelyne Lerut, MD, Yves Vanrenterghem, MD, PhD, and Dirk R.J. Kuypers, MD, PhD

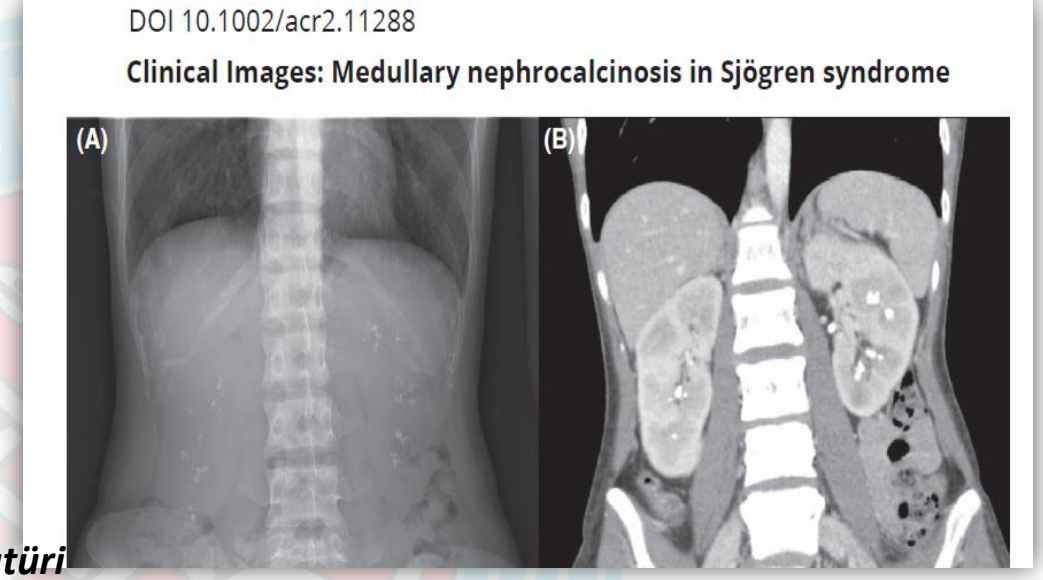
• **A 53-year-old patient with long-standing primary Sjögren syndrome presented with acute renal failure and nephrotic syndrome caused by secondary (AA) renal amyloidosis. Ten years before, he had been admitted because of exacerbation of the systemic disease. At that time, a pseudolymphoma of the kidney was diagnosed. To our knowledge, this is the first report of a patient with primary Sjögren syndrome and secondary (AA) amyloidosis with amyloid deposition in the kidneys causing nephrotic syndrome.** ***Am J Kidney Dis*** **46:E75-E80.**

Renal Lenfoma

- SS' da artmış lenfoma sıklığı (5x ila 16x)
  - Düşük dereceli marjinal zone B lenfoma (en sık), diffüz büyük B hücreli lenfoma (ikinci sıklıkta), Non Hodgkin Lenfoma özelliklede mukoza ilişkili lenf dokusunun (MALT) lenfoması
- Renal lenfoma
  - Daha çok sekonder
  - SS seyrinde primer renal lenfoma tutulumu bildirilen olgu raporları mevcuttur.
- Renal kitle tespit edilen Sjogren vakalarında nötropeni, kriyoglobulinemi, C4 düşüklüğü, vaskülit, splenomegali ve lenfadenopati varlığı değerlendirilmeli, lenfoma olabileceği düşünülerek ince iğne aspirasyon biyopsisi, nefrektomiden önceki seçenek olmalıdır.

Patel ve ark. J Rheumatol. 2013:102-103

Nefrolityazis



- %10-%20
- ***distal RTA'da gelişen hiperkalsiüri ve hipositratüri***
  - Asideminin bir sonucu olarak, kalsiyum fosfat kemikten salınır ve alkali idrarda çökeltilir.
  - Sitrat kalsiyum içerikli taş oluşumu için inhibitördür, bu nedenle hipositratüri kalsiyum içerikli taş oluşumunu tetikler.
- ***Akut böbrek yetmezliği ile başvuran SS hastalarında obstrüktif üropati dışlanmalıdır***

Tedavi

- Tedavide ilk hedef böbrek fonksiyon kaybının ilerlemesine engel olmaktır.
  - Düzenli monitörizasyon
  - Tansiyon regülasyonu
  - Proteinürinin minimalize edilmesi
  - Sigaranın bıraktırılması
- SS ile ilişkili böbrek hastalığının tedavisi, hastalık sürecine, tutulum tipine bağlıdır.

Kontrollü çalışma mevcut değil

- TIN
  - Bikarbonat ve elektrolit takviyesi
  - KS, Kalsinörin inhibitörleri, CTX ve MMF
  - Gözlemler tek başına KS yerine kombinasyon
  - Dozlar ve süre?
  - MMF ve CTX (şu an kullanımı tavsiye edilmiyor) en sık denenenler

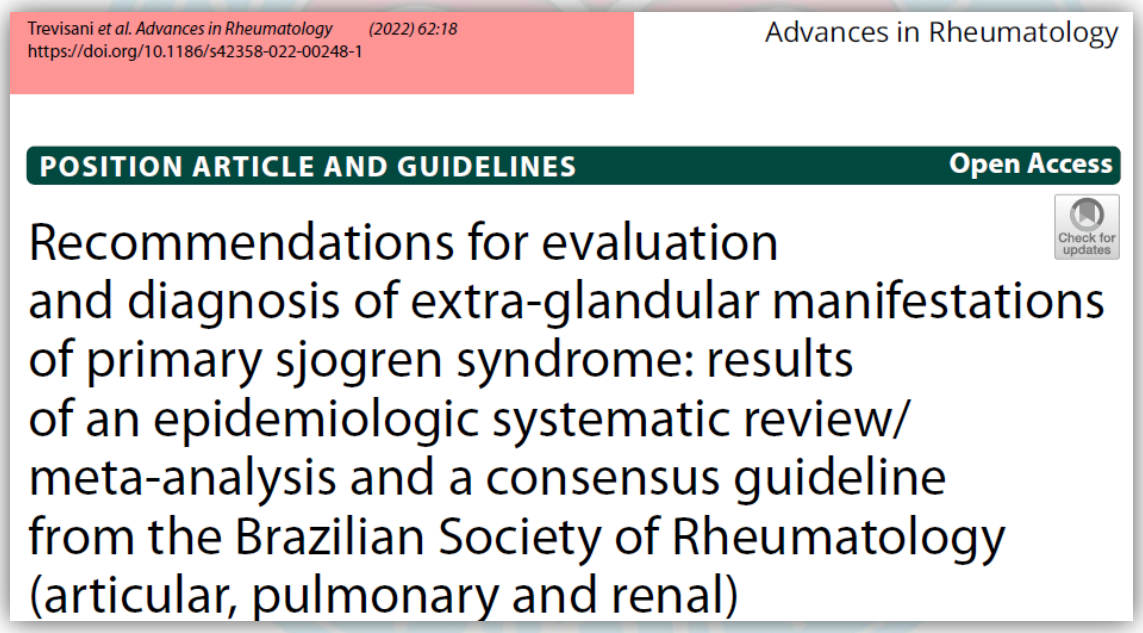
- GN
  - Eşlik eden hipertansiyon ve proteinüri tedavisi için optimum dozda Angiotensin II reseptor blokörleri
  - MPGN: Pulse ve sonrası yüksek doz KS, remisyonda AZA veya CTX, diğer seçenekler MMF, RTX ve plazma değişimi
  - KV: Pulse, yüksek doz KS, plazma değişimi ve RTX

Prognoz

- Uzun vadeli prognoz, klinik olarak anlamlı böbrek tutulumu olan SS'li hastalar için değişkendir
- Biyopsi tanısı alarak izlenen hasta serilerine dayanarak ***son dönem böbrek yetmezliğine ilerleme % 10-20***
- ***3 yıllık renal sağkalım TİN grubunda %100, glomerülonefrit grubunda %66***
- ***GN tutulumlu hastalar interstisyel nefritli hastalara göre yüksek lenfoma geliştirme riski altındadır ve sağkalımları daha kötüdür***.
- ***Glomerülonefrit, tubulointerstisyel nefrite göre daha yüksek mortalite ile ilişkili***

Kidder D ve ark. Nephrol Dial Transplant. 2015;30:1363-9
Goules ve ark. Arthritis and Rheumatism. 2013:2945-2953
Goules ve ark. Medicine. 2000:241-249

(6) Renal manifestations are underdiagnosed, as they do not often present evident symptoms; thus, an adequate and systematic assessment of renal function is required. When investigating, we must consider the two types of renal impairment: distal tubulointerstitial nephritis (Type I) and proximal tubulointerstitial nephritis (Type II), with or without renal tubular acidosis (RTA); and glomerulonephritis (GN).; (Level of Agreement: 100%, Strength of Recommendation: Strong)


Trevisani *et al. Advances in Rheumatology* (2022) 62:18
https://doi.org/10.1186/s42358-022-00248-1

Advances in Rheumatology

POSITION ARTICLE AND GUIDELINES Open Access

Recommendations for evaluation and diagnosis of extra-glandular manifestations of primary sjogren syndrome: results of an epidemiologic systematic review/meta-analysis and a consensus guideline from the Brazilian Society of Rheumatology (articular, pulmonary and renal)

(6) Renal manifestations are underdiagnosed, as they do not often present evident symptoms; thus, an adequate and systematic assessment of renal function is required. When investigating, we must consider the two types of renal impairment: distal tubulointerstitial nephritis (Type I) and proximal tubulointerstitial nephritis (Type II), with or without renal tubular acidosis (RTA); and glomerulonephritis (GN).; (Level of Agreement: 100%, Strength of

(7) Initial and follow-up evaluations are recommended even in asymptomatic patients, with the measurement of serum creatinine, glomerular filtration rate (GFR), type I urine (pH and density always assessed in fresh morning urine), serum electrolytes (Na, K, Cl), venous blood gases (HCO_3, blood pH), and plain abdominal radiography or renal bladder ultrasound. (Level of Agreement: 100%, Strength of Recommendation: Strong)

- Serum kreatinin
- GFR
- İdrar pH ve dansitesi (sabah ve taze)
- Serum elektrolitleri (Na, K, Cl)
- Venöz kan gazı (kan pH ve HCO_3)
- Direkt grafi veya USG (mesane ve böbrek)

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(8) The diagnosis of tubulointerstitial involvement requires an active search for RTA signs and symptoms: cramps, muscle weakness, hypokalemic periodic paralysis, renal lithiasis, nephrocalcinosis, polyuria, polydipsia, nocturia, nephrogenic diabetes insipidus, bone pain, and pathological fractures secondary to osteomalacia. (Additional file 1: Chart S2) In these cases, in addition to the initial laboratory evaluation, serum calcium and phosphorus, 24-h proteinuria, or the protein creatinine index (PCI) should be assessed. Hypocitraturia is a frequent and early finding in distal tubular dysfunction, being a risk factor for urolithiasis and nephrocalcinosis (Level of Agreement: 100%, Strength of Recommendation: Strong)

- RTA semptom ve bulguları açısından sorgula
- Kramplar, kas güçsüzlüğü (HPP), böbrek taşı, nefrokalsinoz (hipositratüri), poliüri, polidipsi ve noktüri (NDİ), kemik ağrısı ve patolojik fraktür (sekonder osteomalazi)
- İdrarda sitrat atılımı4
- Serum kalsiyum ve fosfor
- 24 saatlik idrarda proteinüri

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(9) Distal renal tubular acidosis (dRTA) is secondary to tubulointerstitial nephritis (TIN) when urinary pH > 5.5 in the presence of metabolic acidosis, with normal blood anion gap and positive urinary anion gap. If urinary pH > 5.5 in the absence of metabolic acidosis, incomplete distal renal tubular acidosis (idRTA) should be considered. Urinary acidification tests with ammonium chloride or furosemide and hydrocortisone confirm the diagnosis if urinary pH remains > 5.5. If these tests are not available, the patient should be monitored more frequently. In cases of urinary pH > 7.5, proximal renal tubular acidosis (pRTA) should be suspected, which may course with normal glycosuria and glycemia, hyperphosphaturia, hyperuricosuria, aminoaciduria, hypophosphatemia, and hypouricemia. Assessment of these tests should be required. (Level of Agreement: 100%, Strength of Recommendation: Strong)

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(10) Glomerular involvement is much less frequent, but presents evident symptoms in most cases and may be associated with cryoglobulinemia. (Additional file 1: Chart S2) Laboratory findings are suggestive of impaired kidney function, proteinuria, hematuria, leukocyturia, cylindruria, and hypocomplementemia. Assessment of this test should be required. (Level of Agreement: 100%, Strength of Recommendation: Strong)

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(11) Renal biopsy is indicated for suspected glomerulopathies, cases of tubulointerstitial nephritis with kidney failure or severe electrolyte imbalance, and differential diagnosis. (Level of Agreement: 100%, Strength of Recommendation: Strong)