Clinical Aspects of Proteinuria

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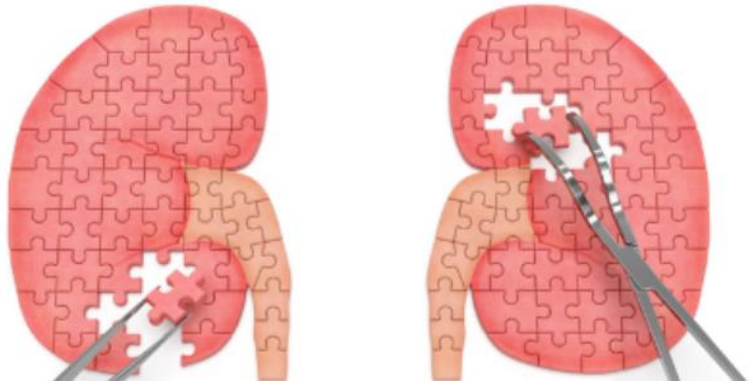
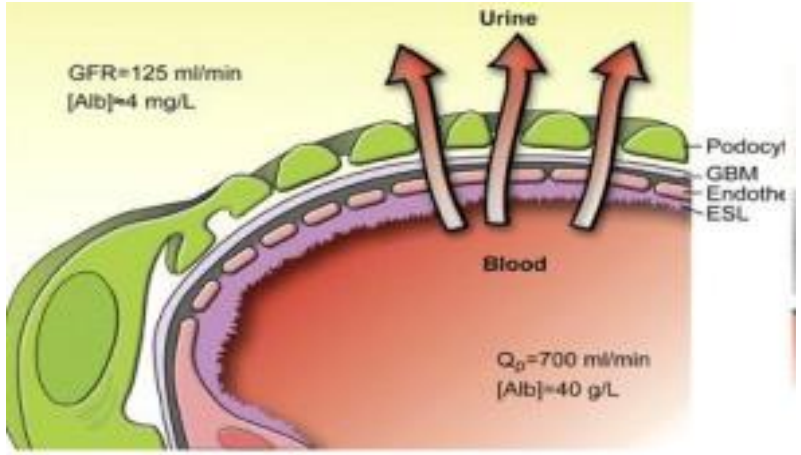
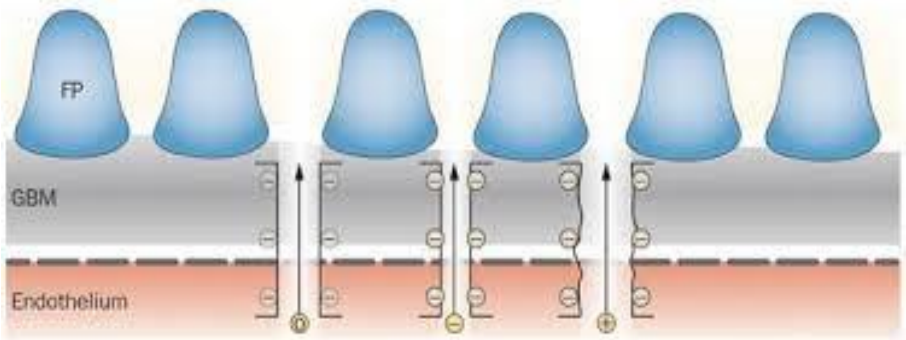


An adult person's urine can contain 150 mg of protein per day (contains wastes, that need to be eliminated from the body)

*Kidney is a smart organ and seperates these proteins, during filtration ★ .

- When the amount is >150 mg/day, we call it proteinuria.





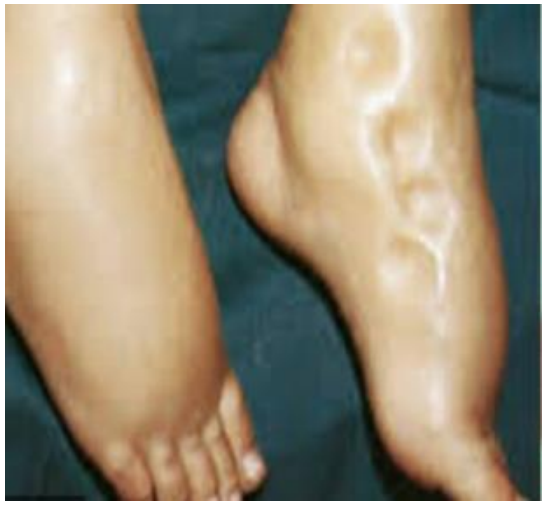
Do you know how old the term proteinuria is?

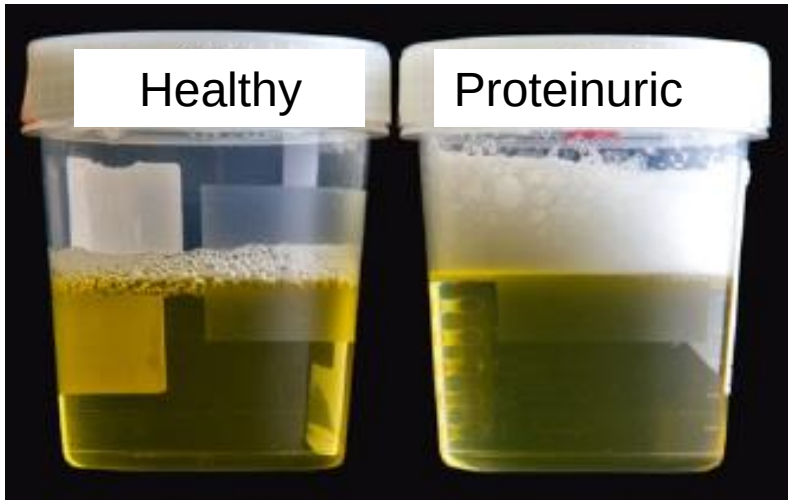
İt’s known since 460-370 BC.

The first recorded proteinuria is

“If the urine is foamy, the kidney may be sick.”

(Hippocrates)





Why Proteinuria is so important?

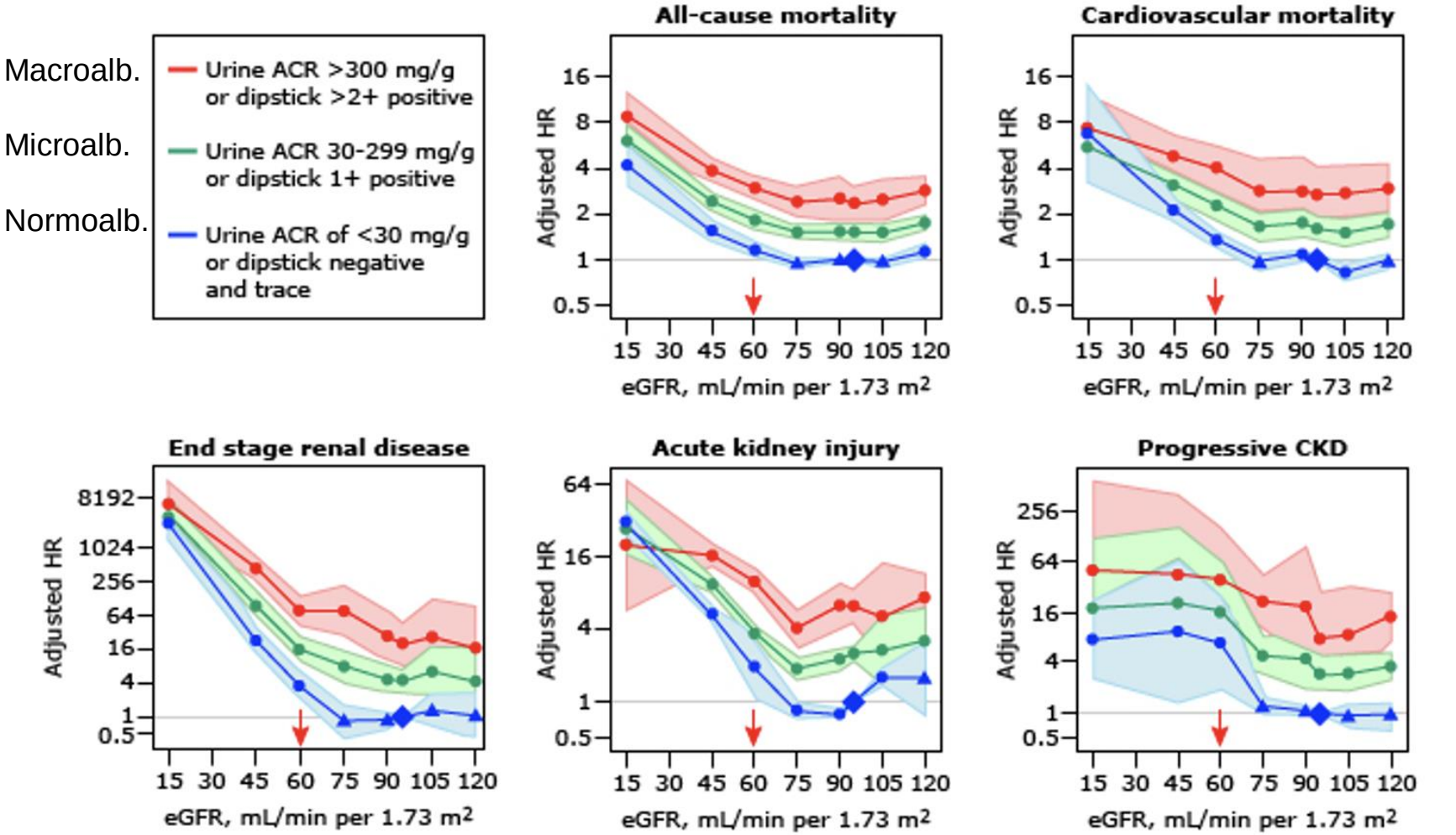
Albuminuria is an important early predictor of heart and kidney disease outcomes

Author	Study type	Population	Test	Outcome measure	Most predictive test
Zhao et al. 2016 [19]	Prospective cohort	438 Chinese patients with IgA nephropathy	UPCR UACR 24 h UPE	Composite of death, RRT or > 30% change in eGFR	UACR
Talreja et al. 2014 [25]	Prospective cohort	207 Canadian kidney transplant recipients	UPCR UACR 24 h UPE 24 h albumin excretion	Transplant loss, doubling of SCr or death	All tests similarly predictive
Methven et al. 2011 [18]	Retrospective cohort	1676 Scottish patients with CKD	UPCR UACR 24 h UPE 24 h-albumin excretion	All-cause death, RRT and doubling of SCr level	UPCR and UACR equal
Lambers Heerspink et al. 2010 [11]	Randomised controlled trial	701 patients with type 2 diabetes mellitus and CKD	UACR 24 h UPE 24 h albumin excretion	Doubling of SCr or ESKD	UACR
Ruggenenti et al. 1998 [26]	Cross sectional longitudinal	Subset study of 98 non-diabetic patients with CKD	UPCR 24 h UPE	eGFR decline Progression to ESKD	Both tests similarly predictive

Meta-analyses showed that; higher amounts of proteinuria, is significantly associated with cardiovascular disease, CKD and all-cause mortality.

Ying et al. BMC Nephrology (2018)

Relative risks of major complications of chronic kidney disease based upon a continuous meta-analysis



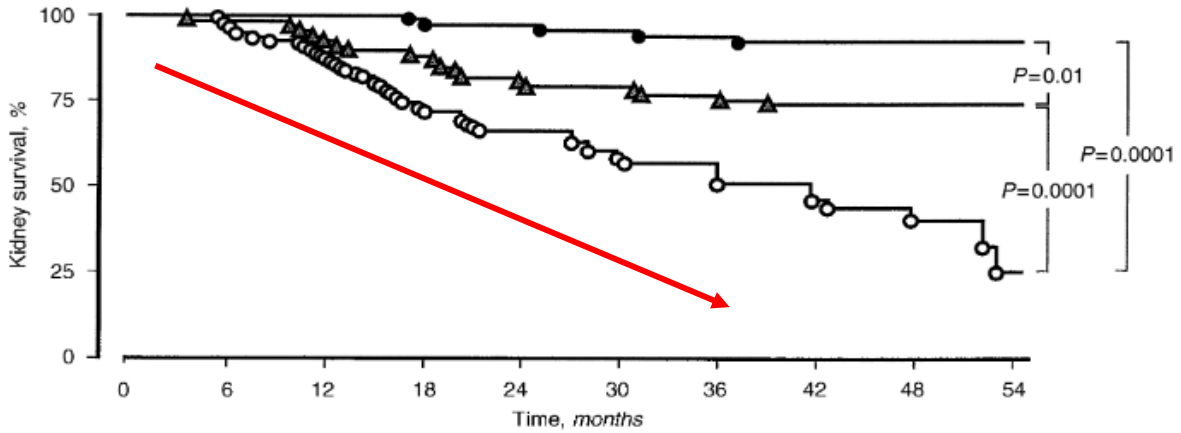
Brad H Rovin, MD, Uptodate, Sep 2023
Ying et al. BMC Nephrology (2018)
Clin Nephrol. 1996;45(5):281.

Proteinuria is a strong marker for CKD progression

directly proportinal

Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies

PIERO RUGGENENTI, ANNALISA PERNA, LIDIA MOSCONI, ROBERTO PISONI, and GIUSEPPE REMUZZI, on behalf of the "GRUPPO ITALIANO DI STUDI EPIDEMIOLOGICI IN NEFROLOGIA" (GISEN)



Number of patients per tertile

Lowest	117	106	102	56	51	42	31	19	14	5
Middle	118	106	91	58	51	39	34	27	19	9
Highest	117	97	81	43	32	24	19	13	10	2

Fig. 2. Progression to end-stage renal failure per tertile of baseline urinary protein excretion rate. Symbols are: (●) lowest; (▲) middle; (○) highest tertile.

The greater amount of PU,

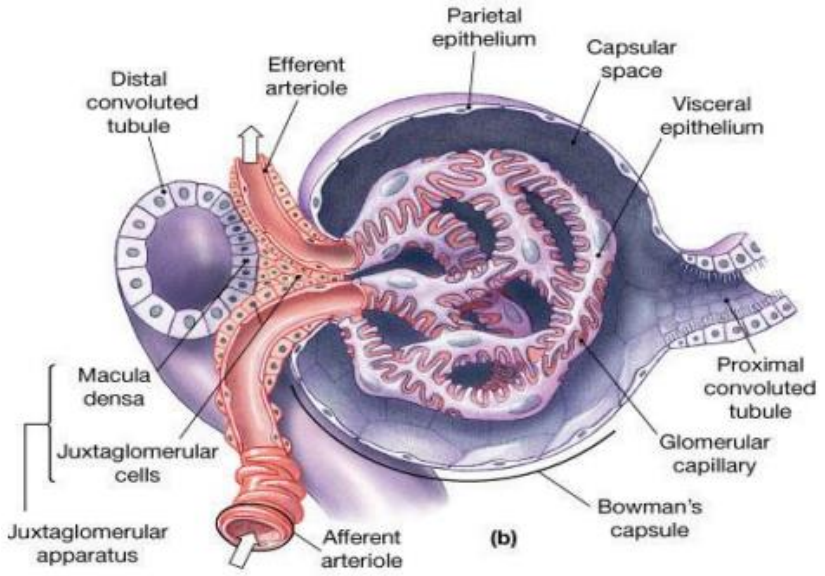
the greater risk of CKD.

Kidney Int. 1998 May;53(5):1209-16.

So, it is very important for us to evaluate proteinuria carefully in a detailed way

The question is; HOW?

Let’s begin to evaluate a patient with proteinuria;



1) Transient proteinuria

- Can occur due to alterations in glomerular hemodynamics

(in conditions such as fever, exercise or in ICU.)

- Proteinuria is generally less than 1 g/day.

No further examination is required,

But annual follow-up will be beneficial.

Robinson RR. Isolated proteinuria in asymptomatic patients. Kidney Int 1980; 18:395

2) Persistent Proteinuria:

Means PU, in at least 2 urine samples (one week apart)

! Further investigation is required.

The underlying disease must be found and treated

Robinson RR. Kidney Int 1980; 18:395

Nat Rev Dis Primers. 2020

How will we detect Proteinuria

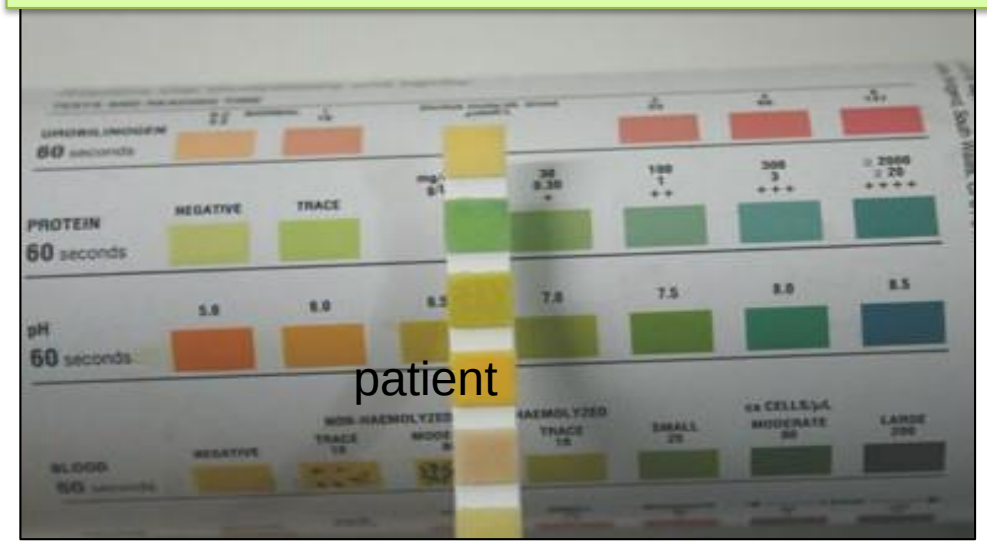
A) Qualitative Methods

1. Dipstick
2. Precipitation of urine proteins with sulfosalicylic acid

B) Quantitative Methods

1. Total protein in 24-hour urine sample
2. Protein /creatinine ratio in spot urine sample

Dipstick; (The most common method for screening patients)



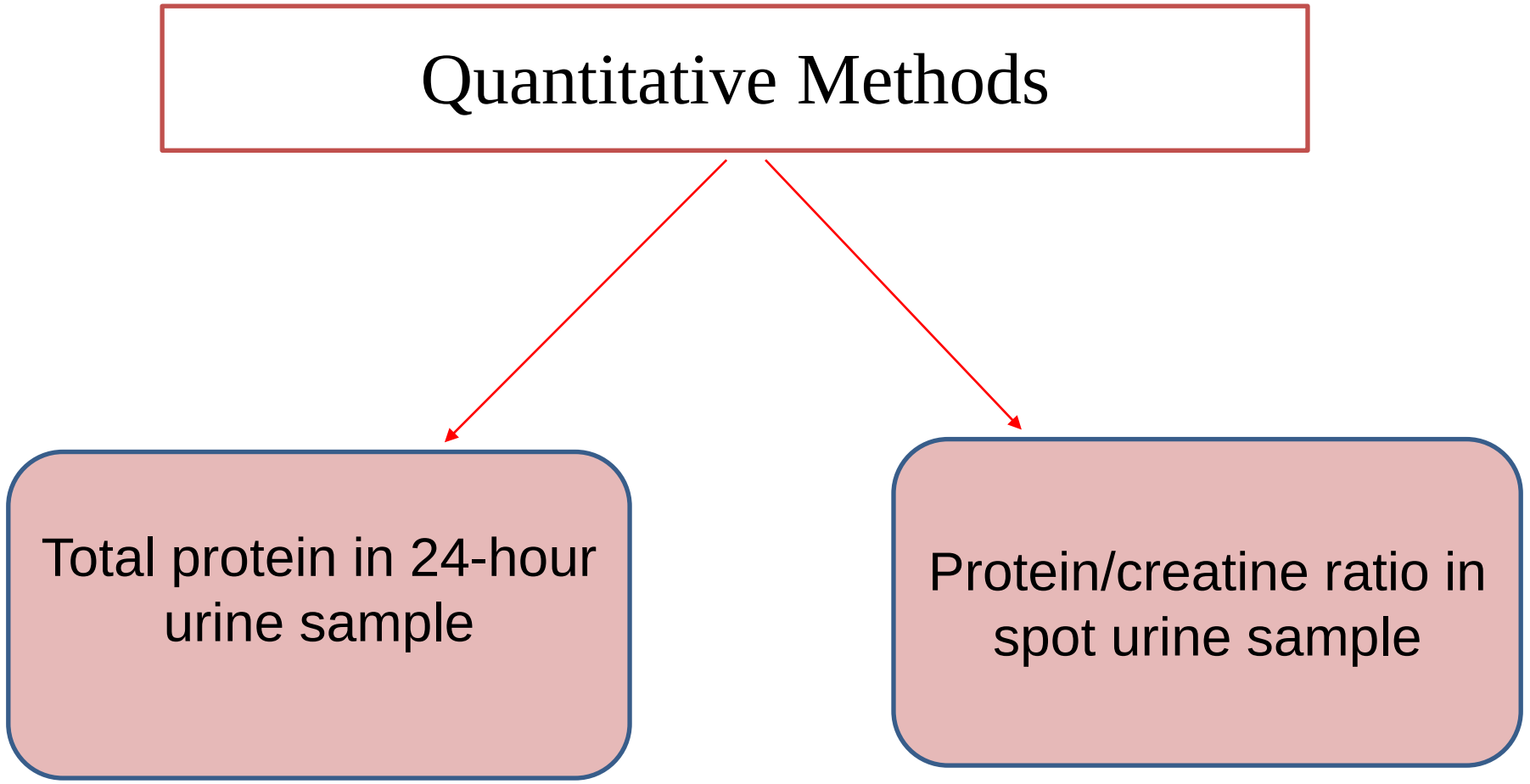
Negative	<10 mg/dl
Trace	10-30 mg/dl
1+	30-100 mg/dl
2+	100-300 mg/dl
3+	300-500 mg/dl
4+	>500 mg/dl

Qualitative Method

Gives result; from + to ++++

(but not in grams)

Quantitative Methods



Gold standart

Used more often (more practical)

PROTEINURIA (+), what about next?

How can we distinguish that, which one our case is?

Evaluation of the Patient with Proteinuria

Anamnesis (systemic diseases, previous history, family history.)

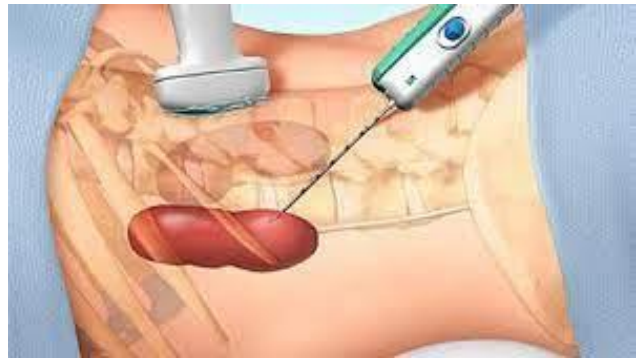
Physical Examination (BP, edema, rash, joint findings)

Advanced Review (Bx and determination of histopathological lesion)

(gold standard in diagnosis)

Kidney International (2021) 100, S1–S276

Renal Biopsy Indications (in adults)



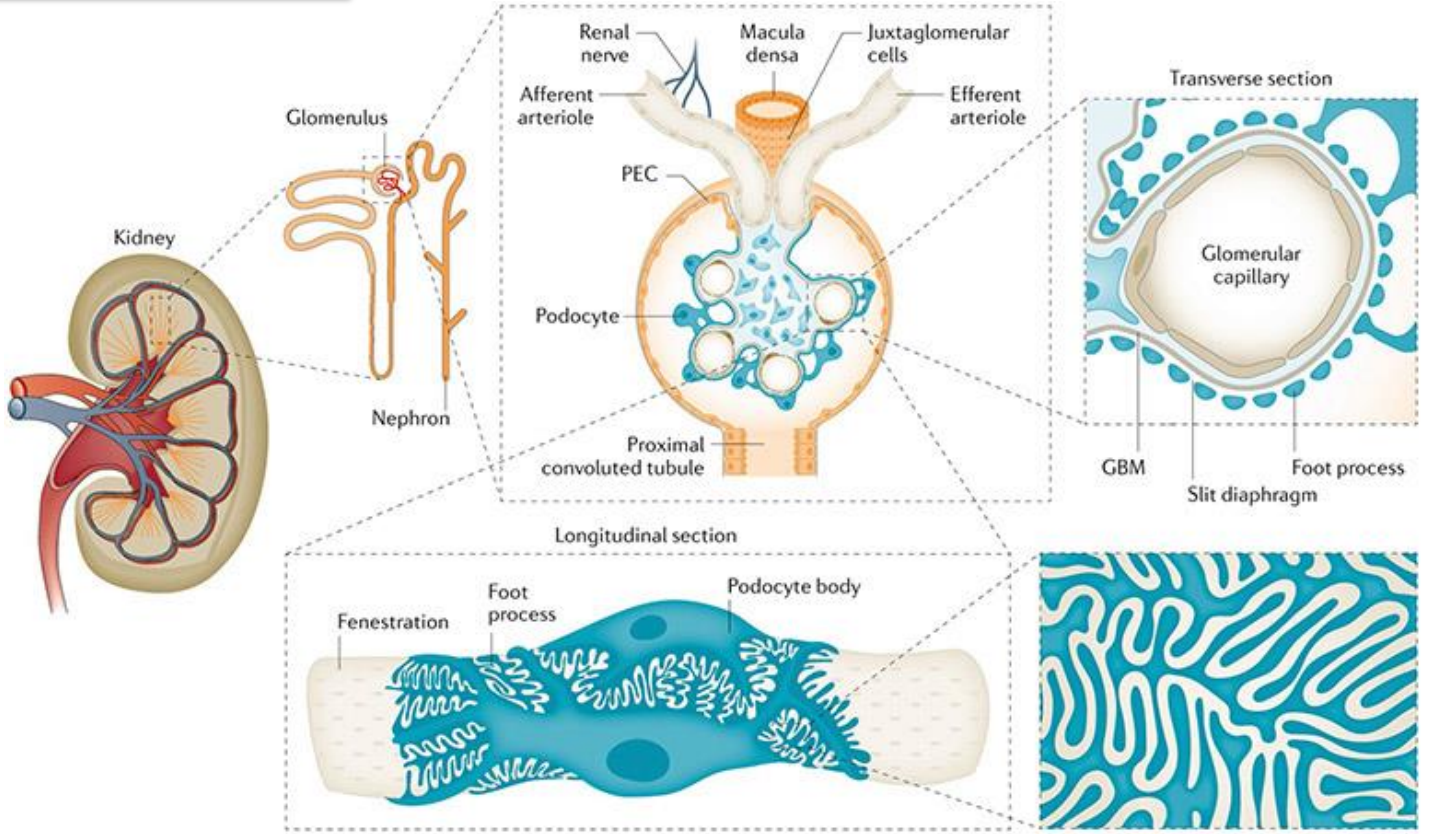
- Unexplained renal failure
- Acute nephritic syndrome *(hematuria, cellular casts, proteinuria, and, frequently, hypertension and kidney function impairment)*
- Nephrotic syndrome
- Isolated nonnephrotic proteinuria *(0.5 to 2 g/day), may not be explained by another condition, such as DM or a known genetic kidney disease.*
- Isolated glomerular hematuria *(persistent microscopic hematuria with dysmorphic red blood cells erythrocyte cast)*

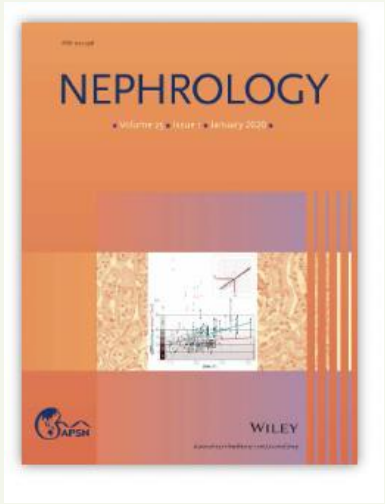
What can we find in the renal Biopsy -Persistent Proteinuria:

We can examine under 4 headings.

1. Glomerular,
2. Tubular,
3. Overflow,
4. Postrenal Proteinuria.

Which is the most common?





3275 biopsies evaluated (for 10 years)

Mean age 33.2 ± 14.2 years.

When patients who underwent biopsy due to PU were examined,

>85 % glomerular causes

5% tubular

< 5% others

Aim

Pattern of kidney diseases varies across geographies due to multiple factors. There is a paucity of information from South Asia due to the absence of nationwide/regional biopsy registries. This study aimed to delineate the spectrum of renal parenchymal diseases in our region.

Methods

immune crescentic GN (24.5%). IgA nephropathy was the commonest etiology of asymptomatic urinary abnormalities (26.3%) and gross haematuria (50%). About 60.9% patients of undetermined chronic kidney disease had glomerular diseases, and 13.6% had chronic tubulointerstitial nephritis. Lupus nephritis and acute cortical necrosis were significantly more common in females compared with males.

Conclusion

This is one of the largest cohorts of kidney biopsies from India, and it delineates the unique features and differences in the pattern of kidney disease in our population.

Nephrology (Carlton). 2020 Jan;25(1):55-62.

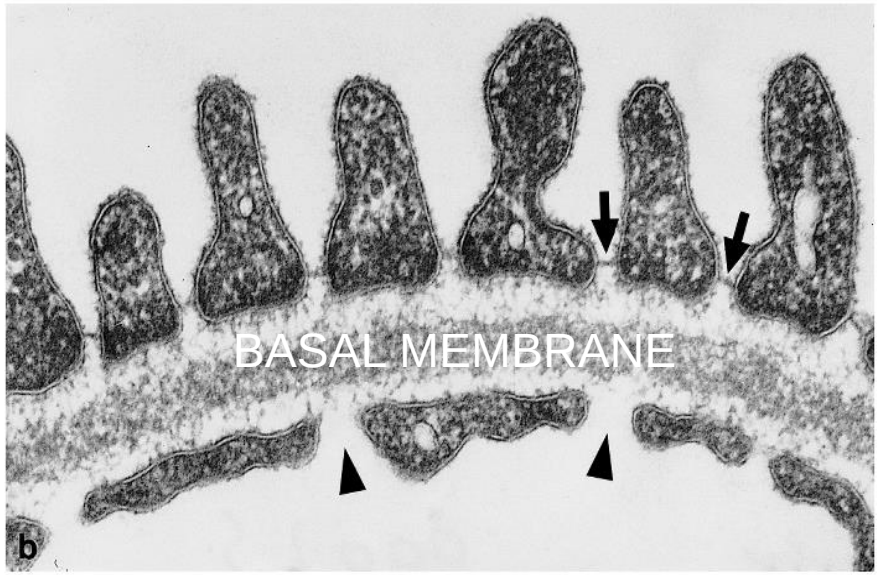
Glomerular Proteinuria

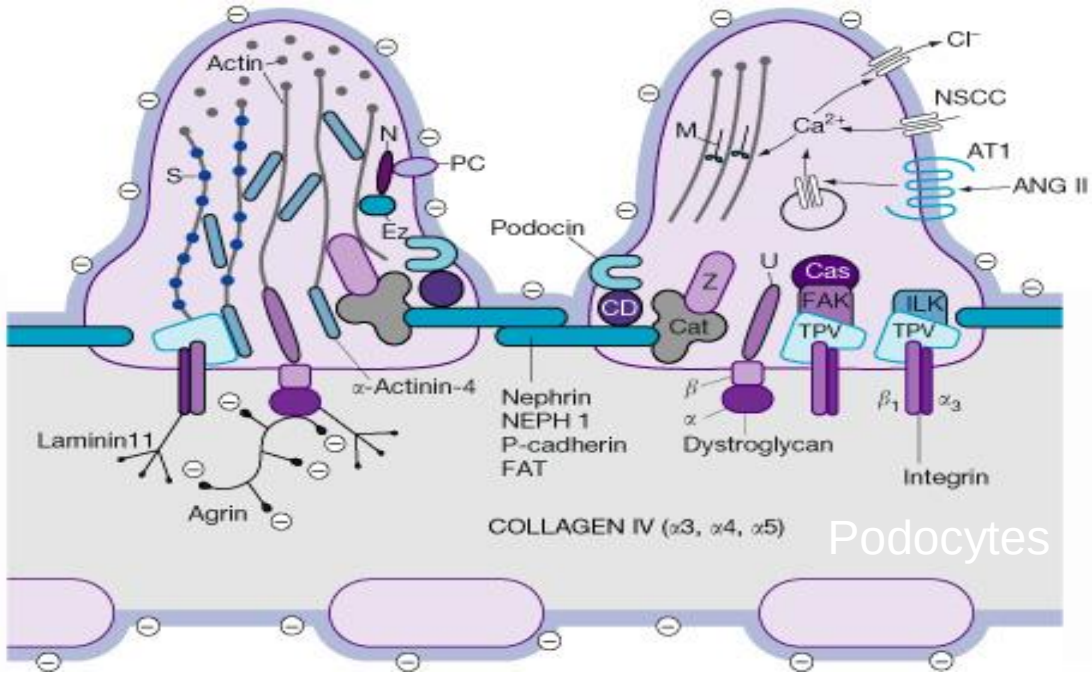
Proteinuria occurs due to damage of any part, that forms the glomerulus

Selectivity is impared and plasma proteins pass into the urine.

CAUSES OF GLOMERULAR PROTEINURIA

PRIMARY (most often)	Membranous nephropathy, Minimal change disease, Focal segmental glomerulosclerosis, IgA Nephropathy, Membranoproliferative glomerulonephritis





Pathophysiology of proteinuria. Kidney Int. 2003
TSN Nephrology Book

CAUSES OF GLOMERULAR PROTEINURIA

PRIMARY (most often)	**Glomerulopathies:** Membranous nephropathy, Minimal change disease, Focal segmental glomerulosclerosis, IgA Nephropathy, Membranoproliferative glomerulonephritis
SECONDARY	**Systemic Diseases:** DM, SLE, Amyloidosis, HUS, Vasculitis
	Infections: Hepatitis B and C, PIGNs, Shunt Nephritis, Endocarditis, HIV
	Drugs: NSAID, Gold Salts, Heroin, Trimethodione, Lithium
	Malignancy: Leukemia, Lymphoma, Solid Organ Cancers
	Other: Renal Artery-Vein Thrombosis, Sickle Cell Anemia

Pathophysiology of proteinuria. Kidney Int. 2003
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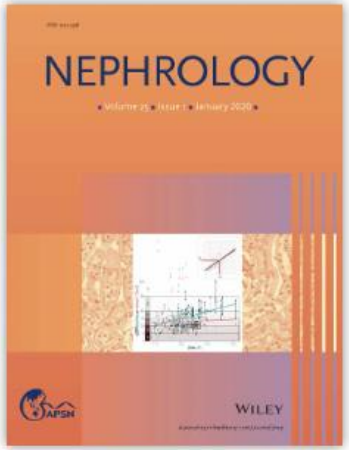
LET'S REMEMBER THE PREVIOUS TRIAL



3275 biopsies evaluated (for 10 years)

Mean age
33.2 ± 14.2 ye

73% primary and

15 % secondary GN.

Among them,

FSGS; was the most common (18.2%)

followed by MCD (16.8%),

MN (16.0%)

IgA nephropathy (10.4%).

Aim

Pattern of kidney diseases varies across geographies due to multiple factors. There is a paucity of information from South Asia due to the absence of nationwide/regional biopsy registries. This study aimed to delineate the spectrum of renal parenchymal diseases in our region.

Methods

artment between 2006 and 2016
e from the available records.

Of the 3275 biopsy evaluated, 61.9% were males, and mean age was 33.2 ± 14.2 years. 6.2% patients were elderly (age ≥ 60 years). Nephrotic syndrome (60.3%) was the commonest indication for biopsy. On histology, 73.0% patients had primary glomerulonephritis (GN), 15.5% secondary GN, 5.3% tubulo-interstitial and 3.7% vascular disease. Focal segmental glomerulosclerosis (FSGS) was the commonest primary GN accounting for 18.2% of all GNs, followed by minimal change disease (16.8%),

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50.9%
3.6%
s were

This is one of the largest cohorts of kidney biopsies from India, and it delineates the unique features and differences in the pattern of kidney disease in our population.

Nephrology (Carlton). 2020 Jan;25(1):55-62.

AJKD AMERICAN JOURNAL OF KIDNEY DISEASES

NATIONAL KIDNEY FOUNDATION®

2,501 patients with primary glomerulonephropathy
were evaluated,
with a mean age 50.6 years.

Am J Kidney Dis. 2016 Oct;68(4):533-544.

Original Investigation

Distribution of Biopsy-Proven Presumed Primary Glomerulonephropathies in 2000-2011 Among a Racially and Ethnically Diverse US Population

John J. Sim, MD,[1] Michael Batech, DrPH,[2] Aviv Hever, MD,[3] Teresa N. Harrison, SM,[2] Taurino Avelar, MD,[1] Michael H. Kanter, MD,[4] and Steven J. Jacobsen, MD, PhD[2]

Background: The incidence and distribution of primary glomerulonephropathies vary throughout the world and by race and ethnicity. We sought to evaluate the distribution of primary glomerulonephropathies among a large racially and ethnically diverse population of the United States.

Study Design: Case series from January 1, 2000, through December 31, 2011.

Setting & Participants: Adults (aged ≥ 18 years) of an integrated health system who underwent native kidney biopsy and had kidney biopsy findings demonstrating focal segmental glomerulosclerosis (FSGS), membranous glomerulonephritis (MGN), minimal change disease (MCD), immunoglobulin A nephropathy (IgAN), and other.

Outcomes: Rates and characteristics of the most common primary glomerulonephropathies overall and by race and ethnicity.

Results: 2,501 patients with primary glomerulonephropathy were identified, with a mean age 50.6 years, 45.7% women, 36.1% Hispanics, 31.2% non-Hispanic whites, 17.4% blacks, and 12.4% Asians. FSGS was the most common glomerulonephropathy (38.9%) across all race and ethnic groups, followed by MGN (12.7%), MCD (11.0%), IgAN (10.2%), and other (27.3%). The FSGS category had the greatest proportion of blacks, and patients with FSGS had the highest rate of poverty. IgAN was the second most common glomerulonephropathy among Asians (28.6%), whereas it was 1.2% among blacks. Patients with MGN presented with the highest proteinuria (protein excretion, 8.3 g) whereas patients with FSGS had the highest creatinine levels (2.6 mg/dL). Overall glomerulonephropathy rates increased annually in our 12-year observation period, driven by FSGS (2.7 cases/100,000) and IgAN (0.7 cases/100,000). MGN and MCD rates remained flat.

Limitations: Missing data for urine albumin and sediment, indication bias in performing kidney biopsies, and inexact classification of primary versus secondary disease.

Conclusions: Among a racially and ethnically diverse cohort from a single geographical area and similar environment, FSGS was the most common glomerulonephropathy, but there was variability of other glomerulonephropathies based on race and ethnicity.

Am J Kidney Dis. 68(4):533-544.

Table 1. Study Population Characteristics by Most Common Primary Glomerulonephropathy Disease States, 2000-2011

	FSGS (n = 973 [38.9%])	MGN (n = 317 [12.7%])	MCD (n = 274 [11.0%])	IgAN (n = 255 [10.2%])	Other[a] (n = 682 [27.3%])	Total (N = 2,501)	P
Age at index date, y							<0.001
Mean ± SD	51.1 ± 16.21	52.0 ± 15.35	49.9 ± 17.45	42.8 ± 13.23	52.5 ± 17.93	50.6 ± 16.67	
Median	52	52	50	42	54	51	
Range	18.0-91.0	18.0-83.0	18.0-87.0	18.0-84.0	18.0-91.0	18.0-91.0	
Patient sex							0.004
Female	419 (43.1)	130 (41)	136 (49.6)	110 (43.1)	347 (50.9)	1142 (45.7)	
Male	554 (56.9)	187 (59)	138 (50.4)	145 (56.9)	335 (49.1)	1359 (54.3)	
Race/ethnicity							<0.001
Asian, non-Hispanic	129 (13.3)	28 (8.8)	26 (9.5)	73 (28.6)	55 (8.1)	311 (12.4)	
Black, non-Hispanic	217 (22.3)	59 (18.6)	50 (18.2)	3 (1.2)			
Hispanic	325 (33.4)	113 (35.6)	89 (32.5)	105 (41.2)			
Other, non-Hispanic	22 (2.3)	4 (1.3)	16 (5.8)	9 (3.5)			
White, non-Hispanic	280 (28.8)	113 (35.6)	93 (33.9)	65 (25.5)	230 (33.7)	781 (31.2)	
Neighborhood household income[b]							0.03
Mean ± SD, in 1,000's USD	61.1 ± 26.8	62.7 ± 27.0	65.1 ± 28.0	65.8 ± 25.6	64.0 ± 28.2	63.0 ± 27.3	
<$25,000	66 (6.8)	13 (4.1)	17 (6.2)	11 (4.3)			
$25,000-$49,999	341 (35)	111 (35)	70 (25.5)	72 (28.2)			
$50,000-$99,999	487 (50.1)	157 (49.5)	160 (58.4)	147 (57.6)			
≥$100,000	79 (8.1)	36 (11.4)	27 (9.9)	25 (9.8)			
History of hypertension	734 (75.4)	195 (61.5)	153 (55.8)	156 (61.2)			
History of diabetes	274 (28.2)	51 (16.1)	38 (13.9)	30 (11.8)			
Body mass index							<0.001
No. with data	681	203	112	219	379	1,594	
Mean ± SD, kg/m^2	30.9 ± 7.34	30.2 ± 6.16	31.9 ± 7.93	29.0 ± 6.21	28.7 ± 6.47	30.1 ± 6.97	
≤25 kg/m^2	150 (22)	38 (18.7)	20 (17.9)	57 (26)	117 (30.9)	382 (24)	
25-<30 kg/m^2	200 (29.4)	76 (37.4)	32 (28.6)	84 (38.4)	120 (31.7)	512 (32.1)	
30-≤35 kg/m^2	158 (23.2)	49 (24.1)	27 (24.1)	48 (21.9)	88 (23.2)	370 (23.2)	
>35 kg/m^2	173 (25.4)	40 (19.7)	33 (29.5)	30 (13.7)	54 (14.2)	330 (20.7)	

FSGS was the most common (38.9%)

followed by MN (12.7%),
MCD (11.0%),
IgAN (10.2%)

Am J Kidney Dis. 2016 Oct;68(4):533-544.

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SCIENTIFIC REPORTS

nature research

10-year retrospective study based on 34,630 cases

Spectrum of biopsy proven renal diseases in Central China: a 10-year retrospective study based on 34,630 cases

Ruimin Hu[1], Songxia Quan[1], Yingzi Wang[1], Yali Zhou[1], Ying Zhang[1], Lu Liu[1], Xin J. Zhou[2]✉ & Guolan Xing[1]✉

Chronic kidney diseases have become a major issue worldwide. The spectrum of biopsy proven renal diseases differs between locations and changes over time. It is therefore essential to describe the local epidemiological trends and the prevalence of renal biopsy in various regions to shine new light on the pathogenesis of various renal diseases and provide a basis for further hypothesis-driven research. We retrospectively analyzed 34,630 hospitalized patients undergoing native renal biopsy between January 1, 2009 and December 31, 2018. Indications for renal biopsy and histological diagnosis were analyzed to describe the prevalence of renal biopsy, and changing prevalence between period 1 (2009–2013) and period 2 (2014–2018) were further analyzed. Nephrotic syndrome (NS) was the most common indication for biopsy. Membranous nephropathy (MN, 24.96%) and IgA nephropathy (IgAN, 24.09%) were the most common primary glomerulonephritis (PGN). MN was most common in adults, with IgAN more prevalent in children. Lupus nephritis (LN) was the most common secondary glomerulonephritis (SGN) in adults, while Henöch–Schönlein purpura nephritis (HSPN) in children. The prevalence of MN increased significantly and nearly doubled from period 1 (15.98%) to period 2 (30.81%) ($P = 0.0004$). The same trend appeared with membranoproliferative glomerulonephritis (MPGN), diabetic nephropathy (DN) and obesity-related glomerulopathy (ORG), while the frequencies of minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), LN and hepatitis B associated glomerulonephritis (HBV-GN) significantly decreased between the two intervals. NS was the most common indication for biopsy across all age groups and genders. MN has overtaken IgAN to become the most common PGN in adults, while IgAN was the most common PGN in children. LN was the most common SGN in adults, and HSPN the most common in children.

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SCIENTIFIC REPORTS

nature research

Spectrum of biopsy proven renal diseases in Central China: a 10-year retrospective study based on 34,630 cases

Ruimin Hu[1], Songxia Quan[1], Yingzi Wang[1], Yali Zhou[1], Ying Zhang[1], Lu Liu[1], Xin J. Zhou[2]✉ & Guolan Xing[1]✉

Both; MN, 24.96% and IgA nephropathy (24.09%)

were the most common primary glomerulonephritis

I would like to point out that,

The distribution and incidence of the primer glomerulonephropathies ***vary across countries, race and ethnic groups.***

TUBULAR PROTEINURIA

Low-molecular-weight proteins are filtered and then almost completely reabsorbed in the tubules.

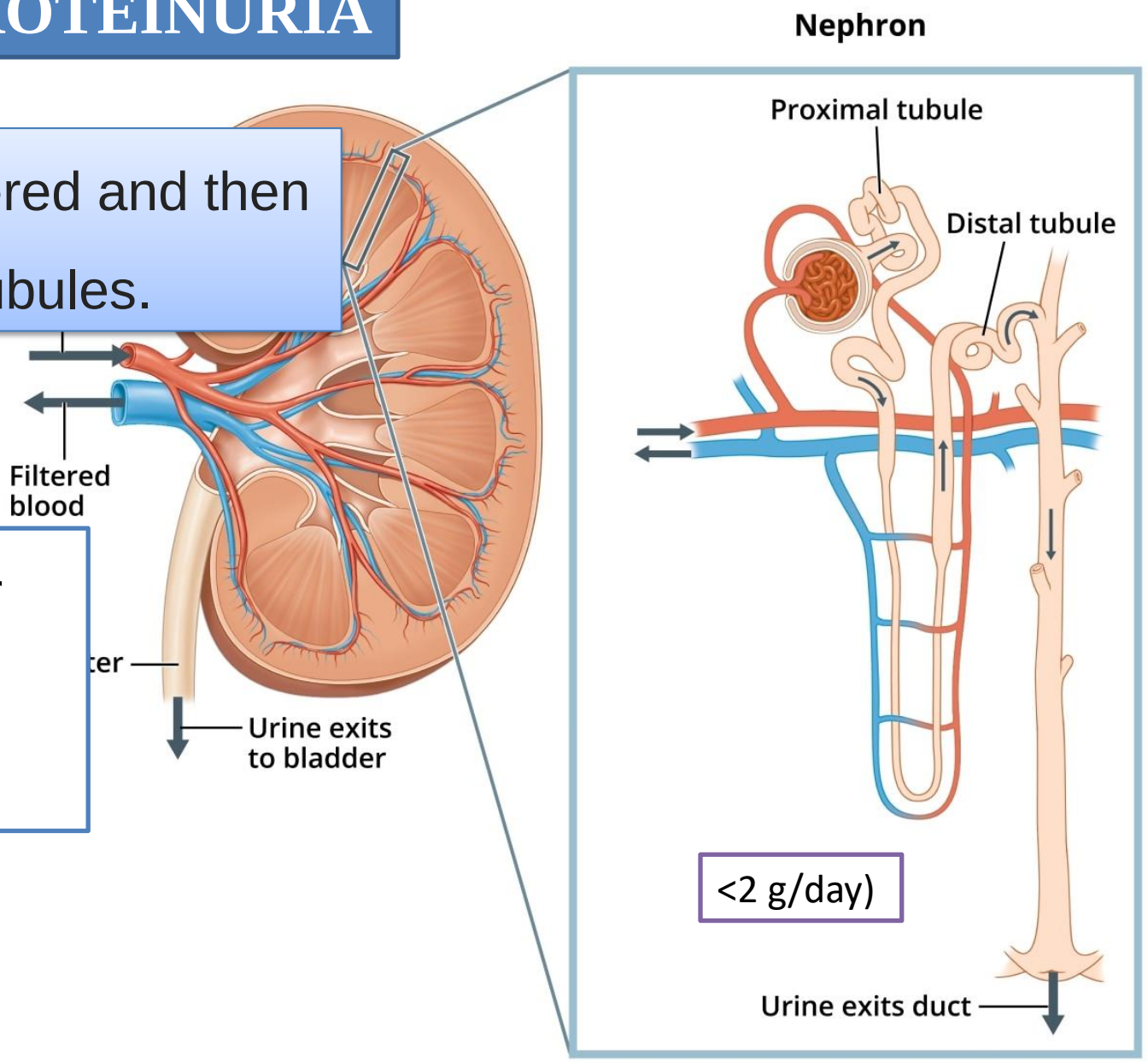
An existing tubular disease, can impair this reabsorption

And Proteinuria occurs

Beta2-microglobulin,

immunoglobulin light chains,

retinol-binding protein, etc



Pathophysiology of proteinuria. Kidney Int. 2003

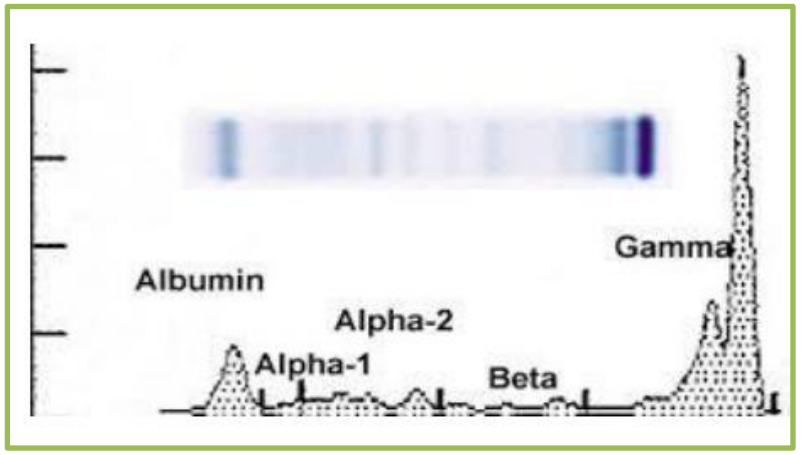
2. TUBULAR PROTEINURIA

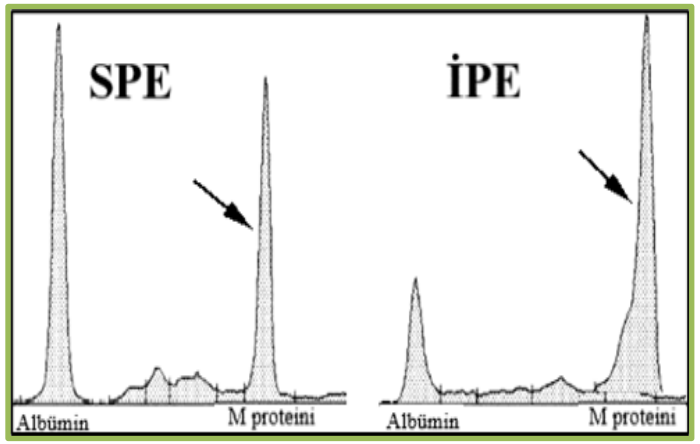
HEREDITARY	PKD, Oxalosis, Wilson's Disease, Fanconi Syndrome and etc.
ACQUİRED	**Acute and chronic interstitial nephritis** (Drugs; NSAID, Lithium, Cisplatin, Aminoglycosides etc.)
	Systemic Diseases: SLE, Amyloidosis, Sjögren's Syndrome
	Malignancies: Leukemia, Lymphoma
	Secondary Involvement of Glomerular Diseases
	Other: Obstructive Uropathy, Pyelonephritis, ATN, Fanconi Syndrome, toxications

Pathophysiology of proteinuria. Kidney Int. 2003
TSN Nephrology Book

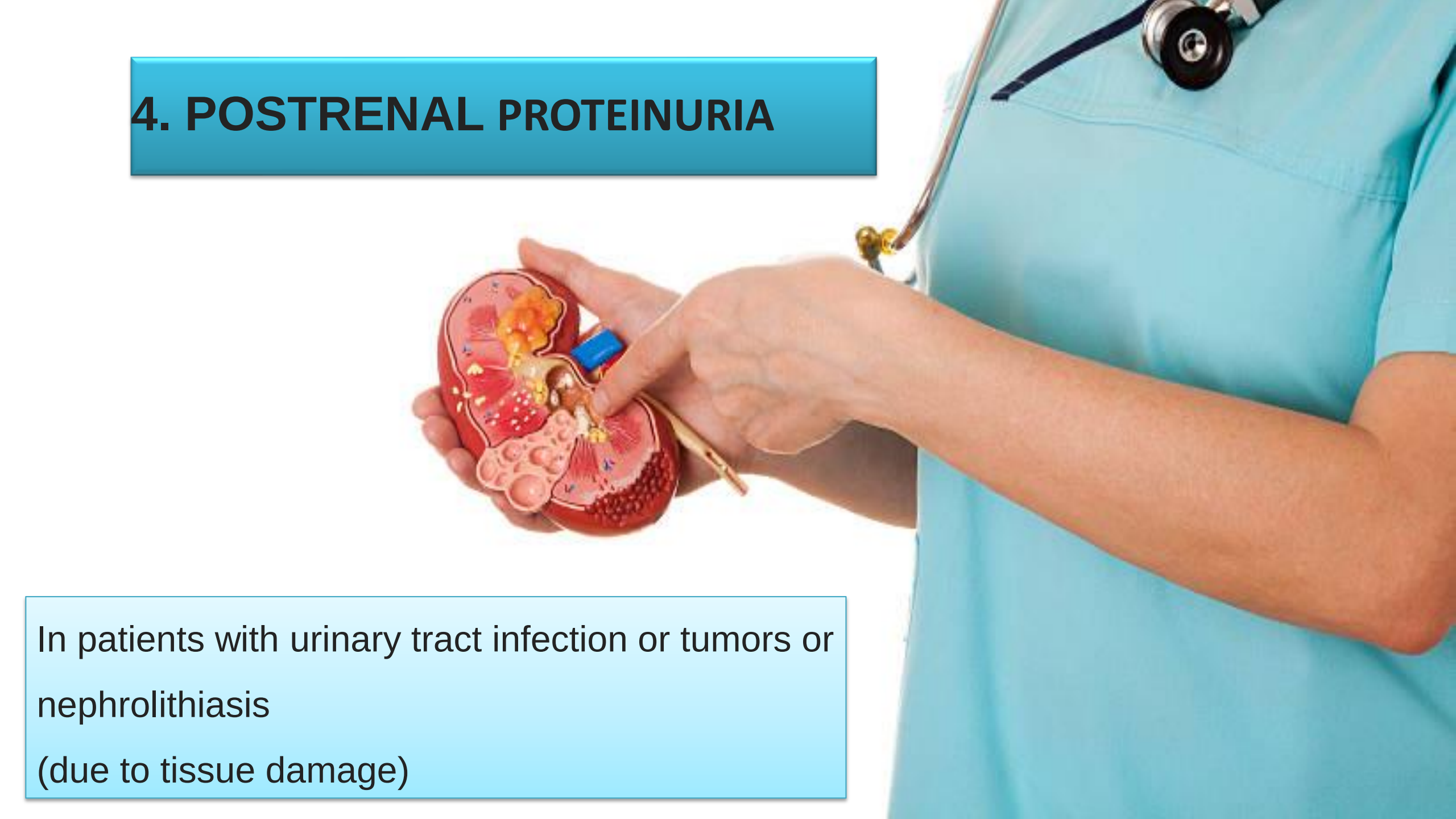
3. OVERFLOW PROTEINURIA

Due to the over-production of low molecular weight protein that exceeding the normal reabsorption capacity (such as myeloma)





4. POSTRENAL PROTEINURIA



In patients with urinary tract infection or tumors or nephrolithiasis

(due to tissue damage)

Treatment (according to the type of PU)

- Tubular PU → Treatment of the systemic disease
- Overflow PU → Consultation regarding primary disease
- Postrenal PU → Urology consultation
- Glomerular PU → The part about us

Treatment

WHEN IT COMES TO TREATMENT

1. Conservative treatment

-Changing Dietary habits

(Decreased protein intake and sodium restriction)

-RAS blockers, SGLT2i, MRAs (Finerenon)

2. Specific treatment

Am Heart J 2008;155:791-805.

29 trials
N = 45 758

Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: A meta-analysis

Saravanan Balamuthusamy, MD, Lavanya Srinivasan, MD, Meenakshi Verma, MD, Sasikanth Adigopula, MD, Nishant Jalandara, MD, Suresh Hathiwala, MD, and Earl Smith, MD, FASN *Chicago, IL*

Objective The role of renin angiotensin system (RAS) blockade in controlling hypertension and the positive impact on cardiovascular (CV) outcomes is well known. However, the role of RAS blockade in improving CV outcomes in patients with chronic kidney disease (CKD) is still unclear.

Methods Randomized controlled trials that analyzed CV outcomes in patients with CKD/proteinuria treated with RAS blockade (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) were included in our study. The relative risk across all study groups was computed using Mantel-Hanszel random effects model. Results were calculated with 95% CI and was considered statistically significant if 2-sided α error was <.05. Renin angiotensin system blockade–based therapy was compared with placebo and control (β-blocker, calcium-channel blockers and other antihypertensive-based therapy) therapy in the study.

Results Twenty-five trials (N = 45758) were used for analysis. Renin angiotensin system blockade decreased the risk for heart failure in patients with diabetic nephropathy when compared with placebo 0.78 (95% CI 0.66-0.92, *P* = .003) and control therapy (0.63, 95% CI 0.47-0.86, *P* = .003). The risk for CV outcomes was decreased with RAS blockade (0.56, 95% CI 0.47-0.67, *P* < .001) in nondiabetic nephropathy patients with CKD when compared with control therapy. There was also a significant reduction of CV outcomes (0.84, 95% CI 0.78-0.91, *P* < .0001), myocardial infarction (0.78, 95% CI 0.65-0.97, *P* = .03), and heart failure (0.74, 95% CI 0.58-0.95, *P* = .02) when we pooled all the patients with CKD and compared RAS blockade to placebo.

Conclusions A pooled analysis of all causes of CKD revealed a reduction in the risk for myocardial infarction, heart failure, and total CV outcomes when RAS blockade was compared with placebo. RAS blockade decreases the risk for CV outcomes and heart failure when compared with control therapy in patients with proteinuria. There were also benefits with RAS blockade in reducing the risk of CV outcomes and heart failure in patients with diabetic nephropathy when compared with placebo. (Am Heart J 2008;155:791-805.)

Am Heart J 2008;155:791-805.

RAS blockers in treatmen

29 trials
N = 45 758

Table I (*continued*)

Study name, year, and N	Methods	ACE/ARB used in study	Comparison drug (control/ placebo)	Mean duration of follow-up	Primary outcome of study	ITA	Study cohort	Mean GFR
Parving[29] 2001 (N = 590)	Prospective randomized double-blinded	Irbesartan	Placebo	22-24 m	Progression of microalbuminuria	Yes	Hypertensive diabetic microalbuminuric cohort	109 ± 2
Rafeal[30] GITS 2001 (N = 241)	Prospective randomized double-blinded	Fosinopril	Nifedepine	3 y	Doubling of serum creatinine/need for dialysis	Yes	Hypertensive, nondiabetic and renal insufficiency	37 ± 20
REIN[31] 1997 (N = 352)	Prospective randomized double-blinded	Ramipril	Placebo	27 m	Decline in GFR	Yes	Hypertensive diabetic nephropathic cohort with protienuria	40.2
RENAAL[32] 2001 (N = 1513)	Prospective randomized	Losartan	Placebo	3.4 y	Doubling of serum creatinine/ESRD/	Yes	Diabetic nephropathy	Albuminuria >1.2 g/d

RAS Blockers decreased the risk for PU; CV risk and CKD progression when compared with placebo

0.78 (95% CI 0.66-0.92, P = .003)

Am Heart J 2008;155:791-805.

KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF GLOMERULAR DISEASES

Practice Point 1.5.1.	Use an ACEi or ARB to maximally tolerated or allowed dose as first-line therapy in treating patients with both hypertension and proteinuria	• Do not stop ACEi or ARB with modest and stable increase in serum creatinine (up to 30%) • Stop ACEi or ARB if kidney function continues to worsen, and/or refractory hyperkalemia • Combinations of ACEi and ARB may be used in young adults without diabetes or cardiovascular disease, but benefits and safety are uncertain Caveat: do not start ACEi/ARB in patients who present with abrupt especially in patients with MCD
Practice Point 1.5.2.	Target syst adult patie standardiz Target 24 h mean arterial pressure in children is ≤50th percentile for age, sex, and height by ambulatory blood pressure monitoring	essure-in-ckd/) as not been validated in GN. In practicality, we are able to achieve an SBP of 120–130 mm Hg in most patients with glomerular disease
Practice Point 1.5.3.	Uptitrate an ACEi or ARB to maximally tolerated or allowed daily dose as first-line therapy in treating patients with GN and proteinuria alone	• Indicated for persistent proteinuria despite treatment of primary GN with immunosuppression (where indicated) • Avoid use of an ACEi or ARB if kidney function is rapidly changing

LET ME REMIND
KDIGO recommends the use of RAS blockers in glomerular diseases guideline

SGLT2i

A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy

see commentary on page 24

OPEN

Immunoglobulin A (IgA) nephropathy is a common form of glomerulonephritis, which despite use of renin-angiotensin-aldosterone-system blockers and immunosuppressants, often progresses to kidney failure. In the Dapagliflozin and Prevention of A Chronic Kidney Disease trial, dapaglifl of kidney failure and prolonged survi with chronic kidney disease with and diabetes, including those with IgA ne Participants with estimated glomerula (eGFR) 25-75 mL/min/1.73m^2 and urir creatinine ratio 200-5000 mg/g (22.6- randomized to dapagliflozin 10mg or placebo, as adjunct to standard care. The primary com site endpoint was a sustained decline in eGFR of 50% more, end-stage kidney disease, or death from a kidney disease-related or cardiovascular cause. Of 270 participants with IgA nephropathy (254 [94%] confirmed by previous biopsy), 137 were randomized to dapagliflozin and 133 to placebo, and followed for median 2.1 years. Overall, mean age was 51.2 years; mean eGFR, 43.8 mL/min/1.73m^2; and median urinary albumin-to-creatinine ratio, 900 mg/g. The primary outcome occurred in six (4%) participants on dapagliflozin and 20 (15%) on placebo (hazard ratio, 0.29; 95% confidence interval, 0.12, 0.73). Mean rates of eGFR decline with dapagliflozin and placebo were −3.5 and −4.7 mL/

progression with a favorable safety profile.

kidney disease, or death from a kidney disease-related or cardiovascular cause. Of 270 participants with IgA nephropathy (254 [94%] confirmed by previous biopsy), 137 were randomized to dapagliflozin and 133 to placebo, and followed for median 2.1 years. Overall, mean age was

Kidney International (2021) **100,** 215–224; https://doi.org/10.1016/j.kint.2021.03.033

KEYWORDS: chronic kidney disease; dapagliflozin; DAPA-CKD; IgA nephropathy; randomized controlled clinical trial; sodium-glucose cotransporter inhibitor

www.kidney-international.org clinical trial

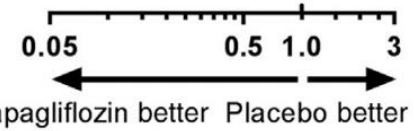
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy

see commentary on page 24

OPEN

SGLT2i were associated with a 71% reduction in PU from baseline

	Dapagliflozin	placebo	Dapagliflozin	placebo		Hazard ratio (95% CI)	Absolute risk difference (95% CI)
	No. of participants/total no.		*Events per 100 patient-years*				
eGFR							
Overall	6/137	20/133	2.5	8.8		0.29 (0.12, 0.73)	-10.7 (-17.6, -3.7)
							-9.2 (-20.0, 1.5)
≥45 ml/min per 1.73 m^2	0/61	8/63	0.0	6.6		0.0 (0.0, ∞)	NC
Urinary albumin-to-creatinine ratio							
Overall	6/137	20/133	2.5	8.8		0.29 (0.12, 0.73)	-10.7 (-17.6, -3.7)
≤1000 mg/g	2/77	5/73	1.5	3.9		0.35 (0.07, 1.8)	-4.3 (-11.0, 2.5)
>1000 mg/g	4/60	15/60	4.0	15.1		0.27 (0.09, 0.82)	-18.3 (-31.0, -5.7)



Kidney Int. 2021 Jul;100(1):215-224.

MRAs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

FIDELIO-DKD ClinicalTrial

5734 patients with CKD and DM with AU

(albumin-to-creatinine ratio of 300 to 5000)

BACKGROUND

Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, reduced albuminuria in short-term trials involving patients with chronic kidney disease (CKD) and type 2 diabetes. However, its long-term effects on kidney and cardiovascular outcomes are unknown.

METHODS

In this double-blind trial, we randomly assigned 5734 patients with CKD and type 2 diabetes in a 1:1 ratio to receive finerenone or placebo. Eligible patients had a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 30 to less than 300, an estimated glomerular filtration rate (eGFR) of 25 to less than 60 ml per minute per 1.73 m^2 of body-surface area, and diabetic retinopathy, or they had a urinary albumin-to-creatinine ratio of 300 to 5000 and an eGFR of 25 to less than 75 ml per minute per 1.73 m^2. All the patients were treated with renin–angiotensin system blockade that had been adjusted before randomization to the maximum dose on the manufacturer's label that did not cause unacceptable side effects. The primary composite outcome, assessed in a time-to-event analysis, was kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes. The key secondary composite outcome, also assessed in a time-to-event analysis, was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.

RESULTS

During a median follow-up of 2.6 years, a primary outcome event occurred in 504 of 2833 patients (17.8%) in the finerenone group and 600 of 2841 patients (21.1%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.93; P=0.001). A key secondary outcome event occurred in 367 patients (13.0%) and 420 patients (14.8%) in the respective groups (hazard ratio, 0.86; 95% CI, 0.75 to 0.99; P=0.03). Overall, the frequency of adverse events was similar in the two groups. The incidence of hyperkalemia-related discontinuation of the trial regimen was higher with finerenone than with placebo (2.3% and 0.9%, respectively).

CONCLUSIONS

In patients with CKD and type 2 diabetes, treatment with finerenone resulted in lower risks of CKD progression and cardiovascular events than placebo. (Funded by Bayer; FIDELIO-DKD ClinicalTrials.gov number, NCT02540993.)

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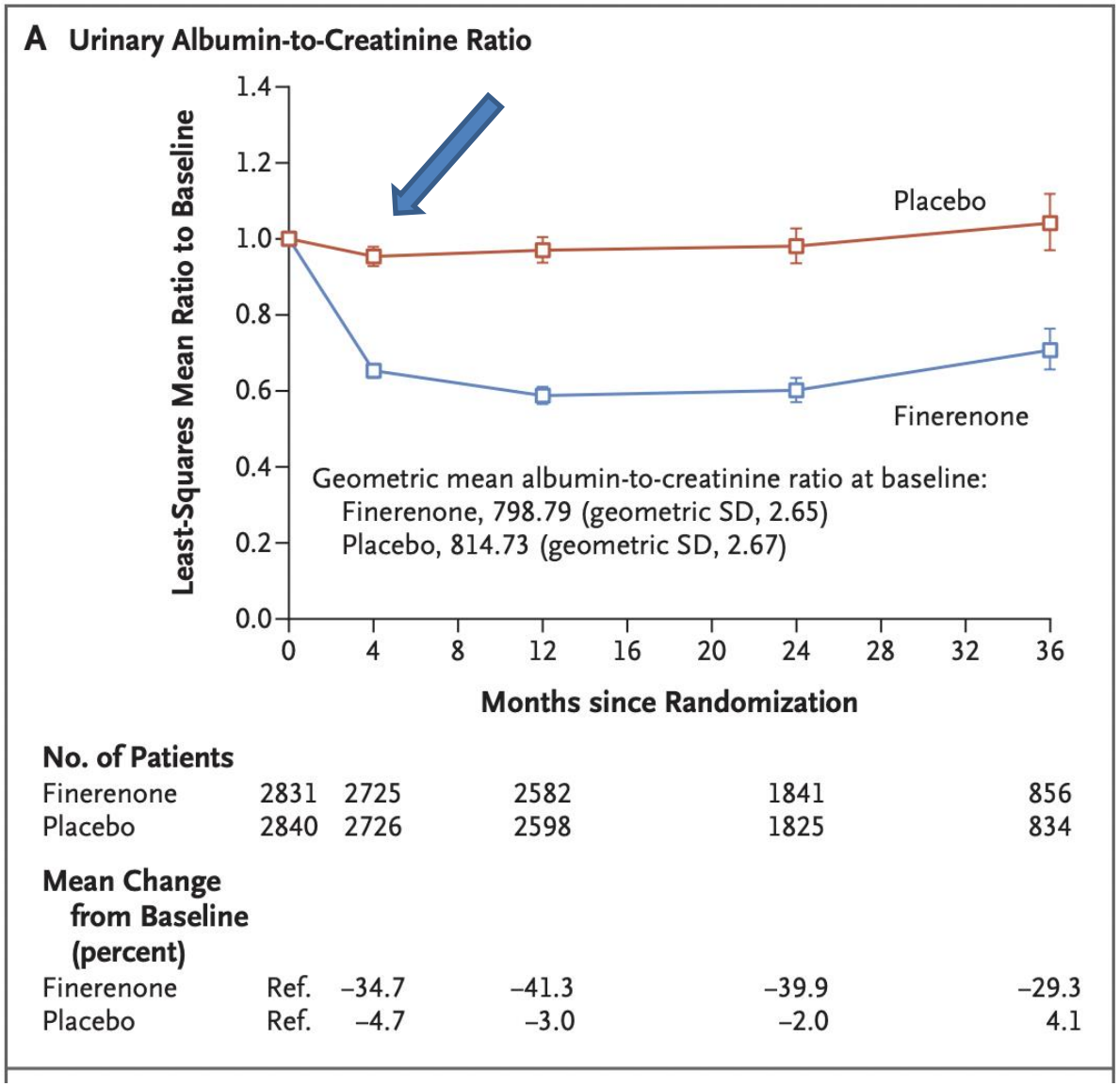
FIDELIO-DKD ClinicalTrial

Finerenone was associated with a 31% reduction in AU in 4 months



No. of Patients					
Finerenone	2831	2725	2582	1841	856
Placebo	2840	2726	2598	1825	834
Mean Change from Baseline (percent)					
Finerenone	Ref.	−34.7	−41.3	−39.9	−29.3
Placebo	Ref.	−4.7	−3.0	−2.0	4.1

KDIGO 2021 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF GLOMERULAR DISEASES

Specific Treatment in Glomerular Proteinuria

- Treatment of underlying cause (drugs, infections and systemic disease)
- Immunosuppressive treatment

  The most recommended treatment is corticosteroid therapy.

  Prednisolone 1 mg/kg/day (max. 80 mg/day) (12-20 weeks)

Kidney International (2021) 100, S1–S276

The other commonly used immunosuppressive agents are:

- Azathioprine
- Alkylating agents (chlorambucil cyclophosphamide)
- Calcineurin inhibitors (cyclosporine, tacrolimus
- Biologics (Rituximab)
- MMF (Mycophenolate mofetil)
- Plasmapheresis

Take to home notes

- Proteinuria is a finding, not a diagnosis.
- But, it is an important prognostic marker.
- The underlying cause must be determined

(and keep in mind some causes may lead to ESRD in the future).

THANKS FOR LISTENING