PROTEINURIA

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WHY SHOULD WE DISCUSS ABOUT PROTEINURIA?

- Marker of renal injury - detected earlier before any decline in GFR
- Detects renal damage and it also promotes RENAL DAMAGE
- Independent risk factor for CARDIOVASCULAR morbidity and mortality
- Help to asses prognosis in pts with CKD

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FRONTIERS IN NEPHROLOGY

How Does Proteinuria Cause Progressive Renal Damage?

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Author Information

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FREE

Metrics

Figure 1: Mechanisms underlying the activation of inflammatory and fibrogenic pathways in proximal tubular epithelial cells by ultrafiltered protein load. As a consequence of proteinuria, the intrarenal activation of the complement cascade may promote injury through the formation of membrane attack complex and biologically active products, such as C3a, that interact with specific receptors. Monocytes/macrophages contribute to fibrosis by release of TGF-β, which stimulates myofibroblast formation and collagen deposition and epithelial mesenchymal transformation. The latter process could be induced in an autocrine manner by TGF-β of proximal tubular cell origin.

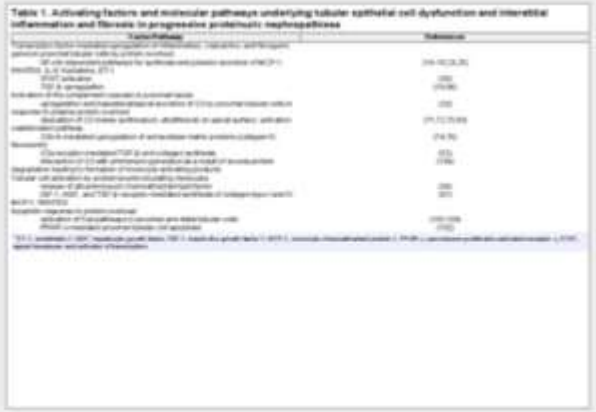
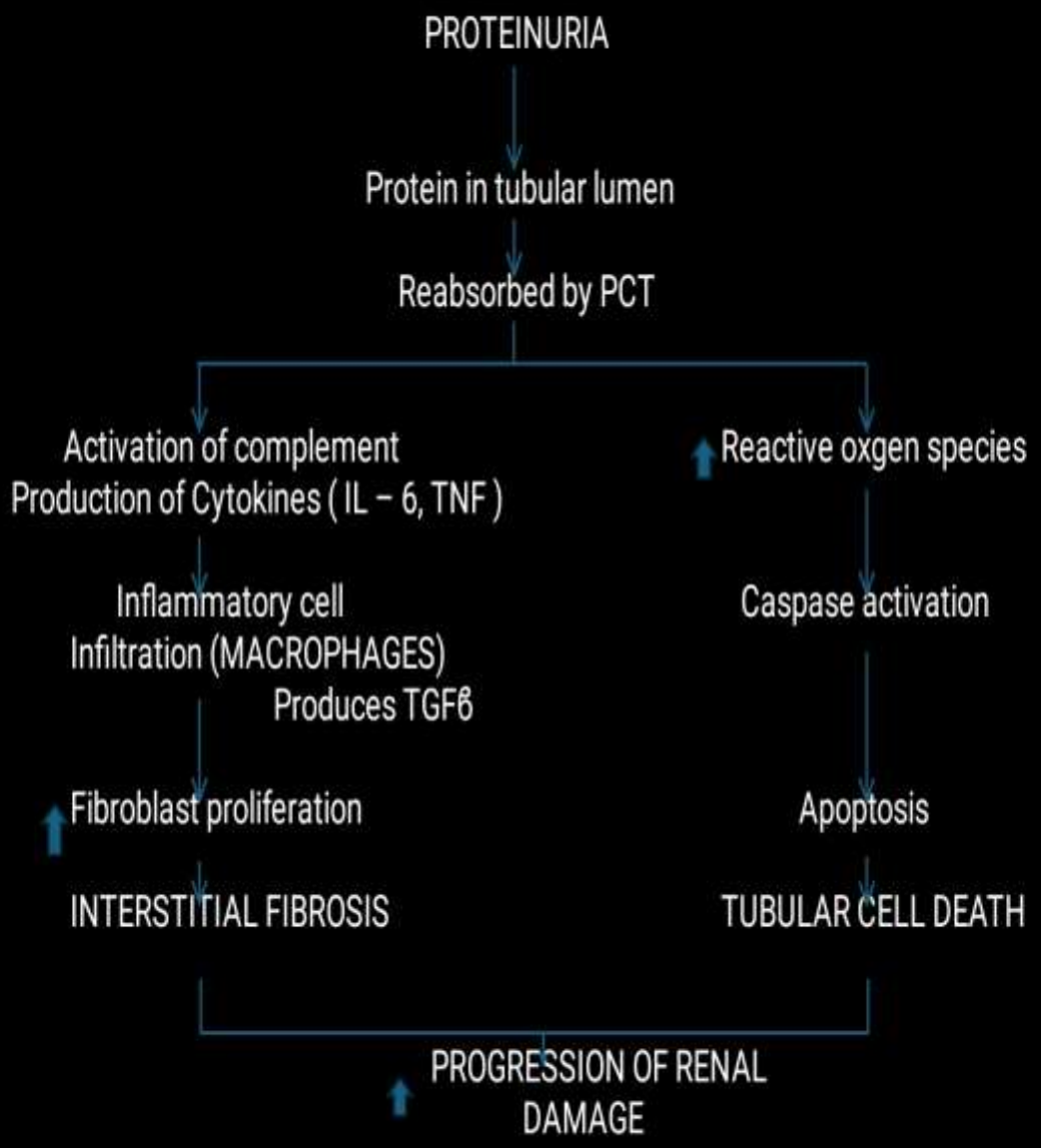


Table 1: Activating factors and molecular

Proteinuria promotes renal damage .



Proteinuria Predicts Stroke and Other Atherosclerotic Vascular Disease Events in Nondiabetic and Non–Insulin-Dependent Diabetic Subjects

Heikki Miettinen, Steven M. Haffner, Seppo Lehto, Tapani Rönnemaa, Kalevi Pyörälä and Markku Laakso

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Stroke. 1996;27:2033–2039

atherosclerotic vascular disease events, in a prospective study of nondiabetic and NIDDM subjects.

Methods Our study was based on the 7-year follow-up of cohorts of nondiabetic (n=1375) and NIDDM (n=1056) subjects in Finland. The urinary protein concentration at baseline was stratified into three categories: no proteinuria (<150 mg/L), borderline (150 to 300 mg/L), and clinical proteinuria (>300 mg/L).

Results The association between the different degrees of proteinuria and the atherosclerotic vascular events was similar in nondiabetic and NIDDM subjects. Cardiovascular disease mortality was higher both in nondiabetic and NIDDM subjects with clinical proteinuria than in those without proteinuria. The incidence of stroke was 1.6% in nondiabetic subjects without proteinuria, 3.2% in subjects with borderline proteinuria, and 8.5% in subjects with clinical proteinuria (P<.001 for trend). In NIDDM patients, the corresponding rates were 7.2%, 11.1%, and 23.0%, respectively (P<.001 for trend). The association between clinical proteinuria and the incidence of stroke remained significant both in nondiabetic and in NIDDM subjects after adjustment for other cardiovascular risk factors. Clinical proteinuria was also associated with the incidence of coronary heart disease events and that of

Proteinuria -Risk factor for cardiovascular diseases

Proteinuria

Increased inflammatory biomarkers
C reactive protein
ADMA(asymmetric dimethyl arginine)

↓

Endothelial damage

↓

Platelet adhesion activation aggregation

↓

Thrombus formation

↓

CAD ,Stroke etc

Physiology of proteinuria

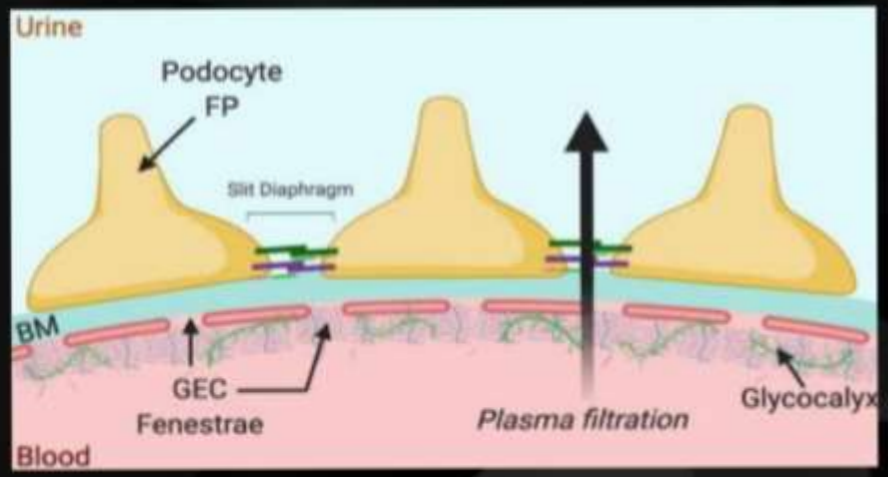
Normally 150mg of protein is excreted in urine per day which contains Tomm horsefall Protein, Albumin(<30mg/d), globulins

Handling of protein is mainly carried out at glomerulus and renal tubules

At Glomeruluar level

Glomerular filtration barrier is a three-layer membrane structure with the following layers (inner to outer):

- Fenestrated glomerular endothelium
- Glomerular basement membrane
- Podocyte



- **@ GLOMERULAR LEVEL**

- **FENESTRATED ENDOTHELIUM** - Restricts RBC and filters out proteins
- **GBM** - charge and size selectivity due to Type 4 collagen,laminin,heparan sulphate
- Restricts protein>100k Dalton and Negatively charged
- **PODOCYTES** -slit diaphragm allows passage of solutes and low molecular weight proteins

@TUBULAR LEVEL

- **PCT** - Reabsorption of LMW proteins and solutes

- **DISTAL PART OF LOOP OF HENLE** - Secretion of Tomm Horsefall protein

CLASSIFICATION OF PROTEINURIA

PROTEINURIA

- TRANSIENT AKA BENIGN
- PERSISTENT

Urine dipstick for protein +ve
24hr urinary protein < 1g / day

Repeat testing after 2 weeks
or
removal of casual factor

Urine dipstick for protein −ve

SUPPORTING POINTS

1) Normal RFT (Signifies Normal GFR)
2) Normal BP
3) Absence of RBC casts, dysmorphic RBC in urine sediment.

TRANSIENT PROTEINURIA

- Transient Proteinuria is a benign condition that resolves after removal of causal factor
- Urinary protein excretion <1g/day
- It occurs due to changes in glomerular hemodynamics mediated by Norepinephrine /Angiotensin 2

- **Causes**
- Fever
- Strenuous exercise
- Emotional stress
- Pregnancy
- UTI
- Exposure to extreme cold

Abstract

The significance of proteinuria during febrile infectious diseases is widely underestimated, although the more marked proteinuria probably signalizes a parainfectious nephropathy rather than a functional disorder. This study shows that mild proteinuria of less than 0.65 g/24 h (normal range less than 0.3 g/24 h using the sensitive tannine-FeCl3-technique) might be caused by the elevated body temperature alone. 9 out of 18 volunteers without renal

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within 12 h. Therefore, the degree of proteinuria during febrile diseases should be considered. Proteinuria of less than 0.5-1 g/24 h in adults might be explained by an altered glomerular function alone. Proteinurias exceeding this value, with a slow regressing tendency will indicate glomerular or tubulo-interstitial diseases, caused possibly by immunologic or toxic products resulting from underlying infectious disease.

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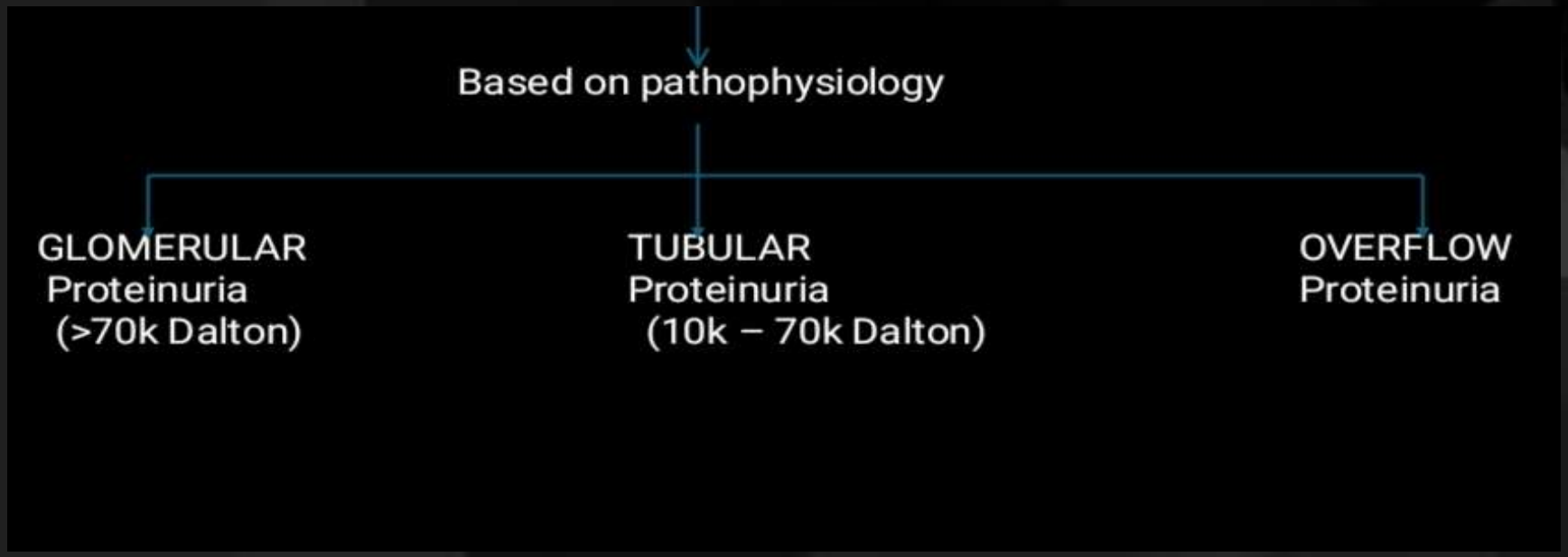
PERSISTENT PROTEINURIA

- If it lasts for > 3months
- Signifies presence of renal pathology
- Early detection and treatment is very important because presence of proteinuria can further cause tubulointerstitial damage and worsen the renal function



PROTEINURIA BASED ON AMOUNT OF PROTEIN EXCRETED

NON NEPHROTIC
Range proteinuria

< 3.5g / day

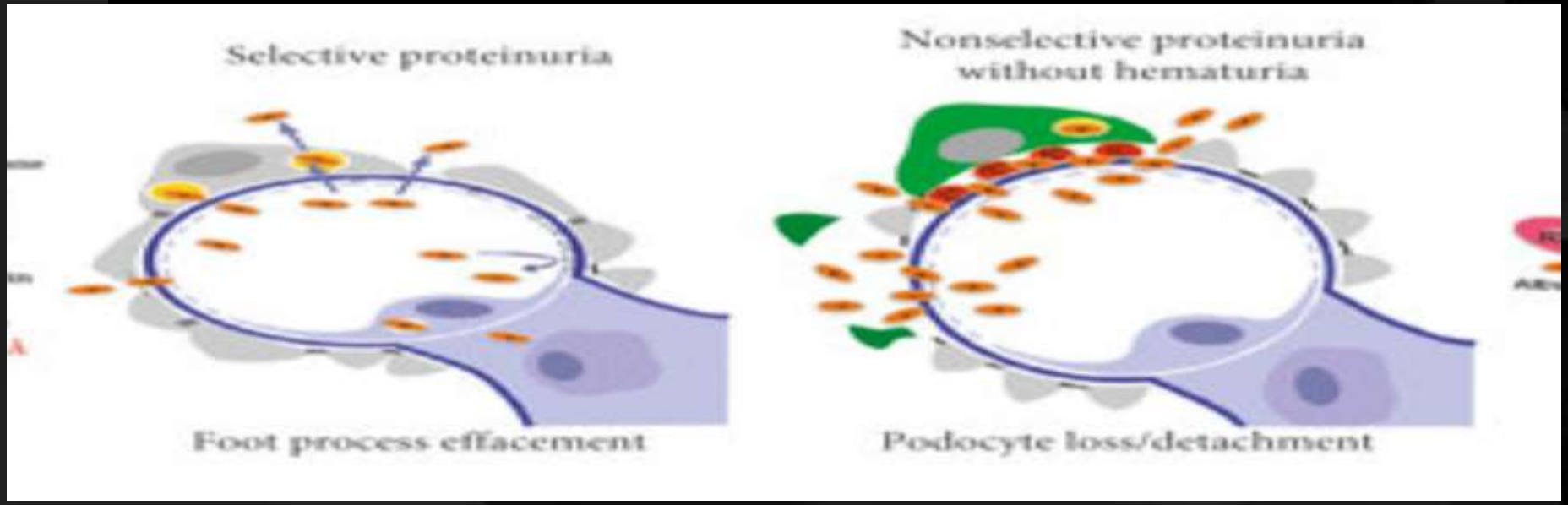
NEPHROTIC
Range proteinuria

> 3.5g / day

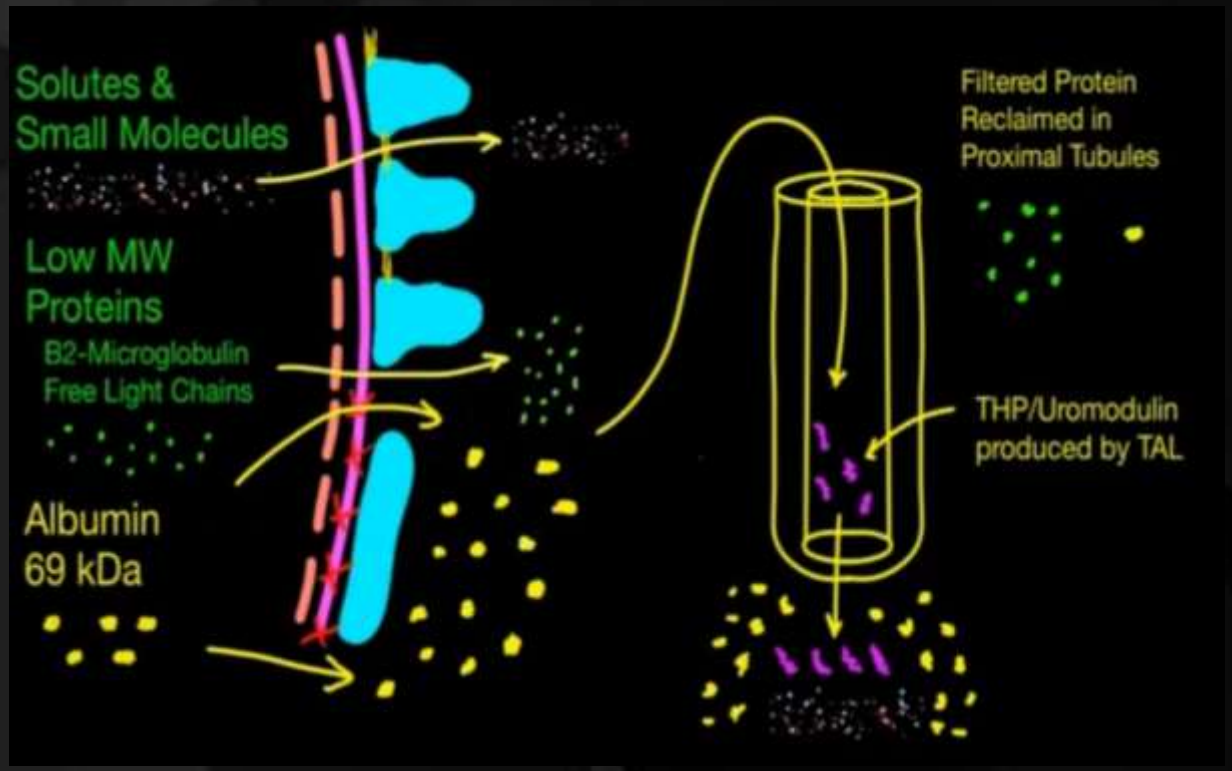
PROTEINURIA BASED ON TYPE OF PROTEIN EXCRETED

SELECTIVE
Proteinuria
Albumin,
Transferrin
(70k -100k Dalton)

NON SELECTIVE
Proteinuria
Albumin, transferrin
IgG, IgA etc.
(>70k Dalton)



GLOMERULAR PROTEINURIA



- Disruption of any component of glomerular filtration barrier
- M/c/c of persistent proteinuria
- Daily urinary Excretion of protein is >2g/day

CAUSES OF GLOMERULAR PROTEINURIA

PRIMARY

- Minimal change disease
- Idiopathic membranous GN
- FSGS
- IgA Nephropathy

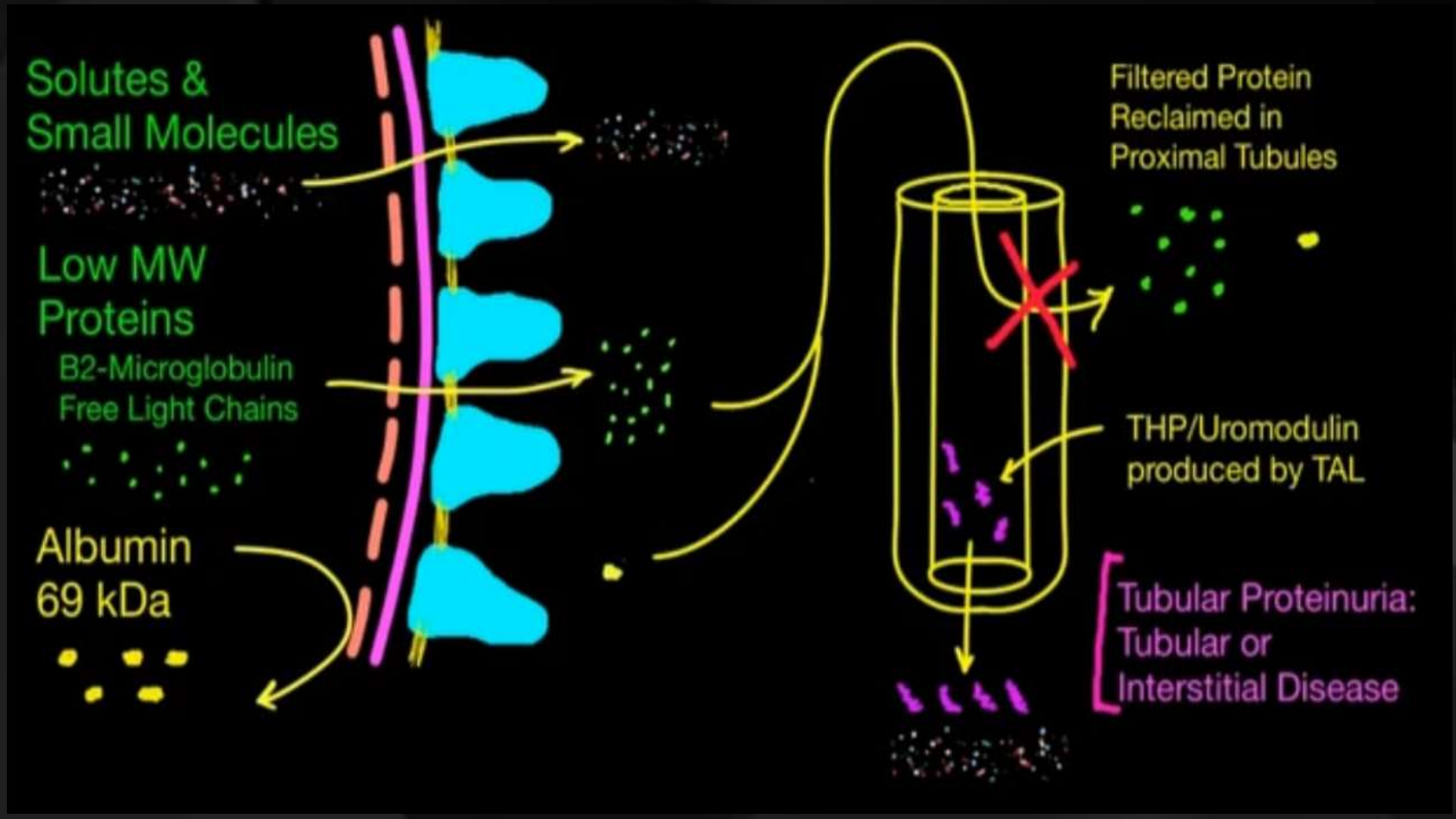
SECONDARY

- Diabetes(MC)
- Connective tissue disorders-Lupus nephritis
- Infections - post streptococcal ,Hep B
- Malignancy - Lyphoma,Lung cancer

- Drug-induced nephropathy (NSAIDs, lithium, heavy metals, heroin
- Hereditary: Alport syndrome

TUBULAR PROTEINURIA

Dysfunction at the proximal tubule resulting impairment of the absorption of filtered proteins

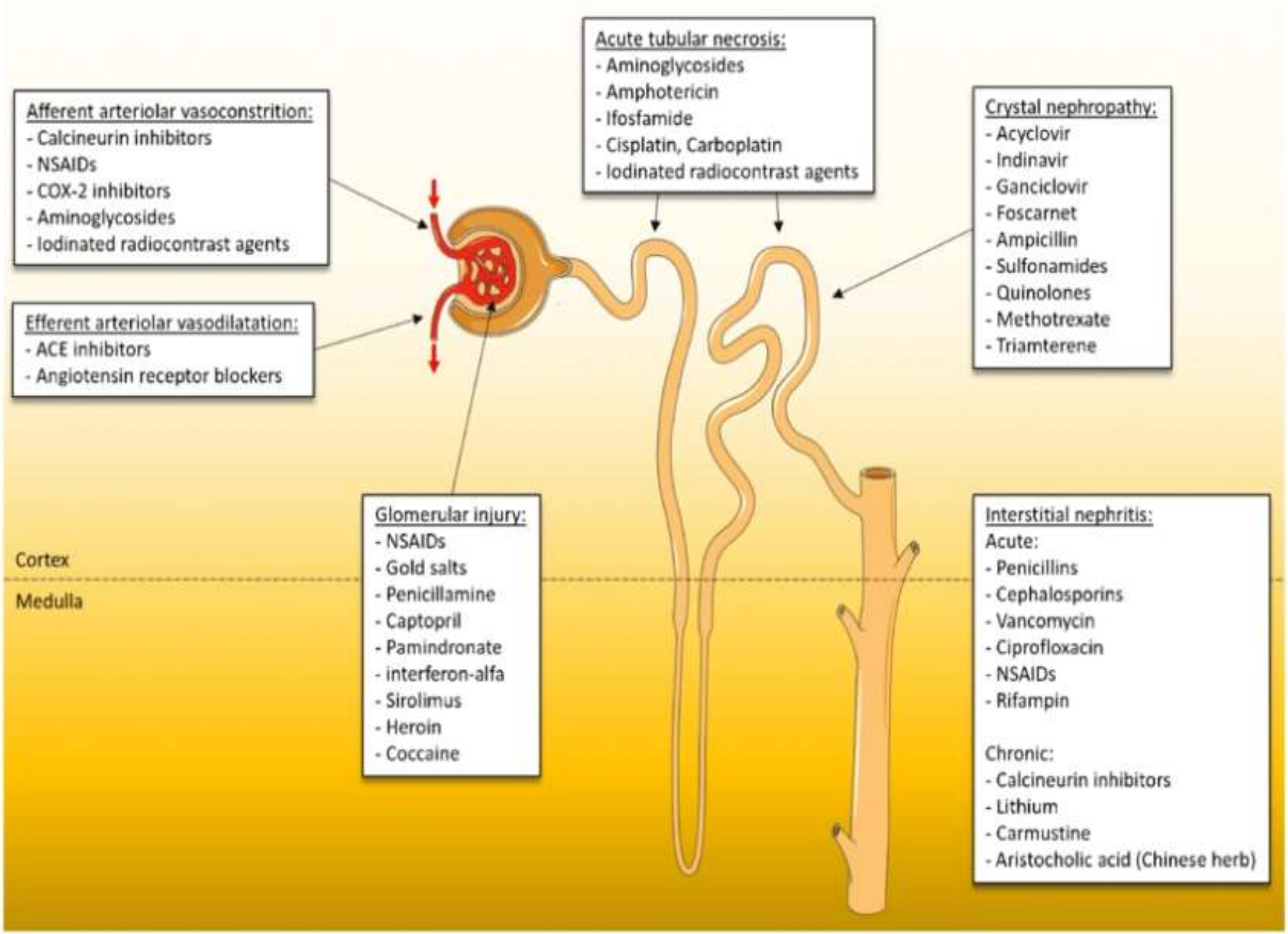


- Protein excretion is less than 2 g/day
- LMW proteinuria
- Not detected in urine DIPSTICK

Causes

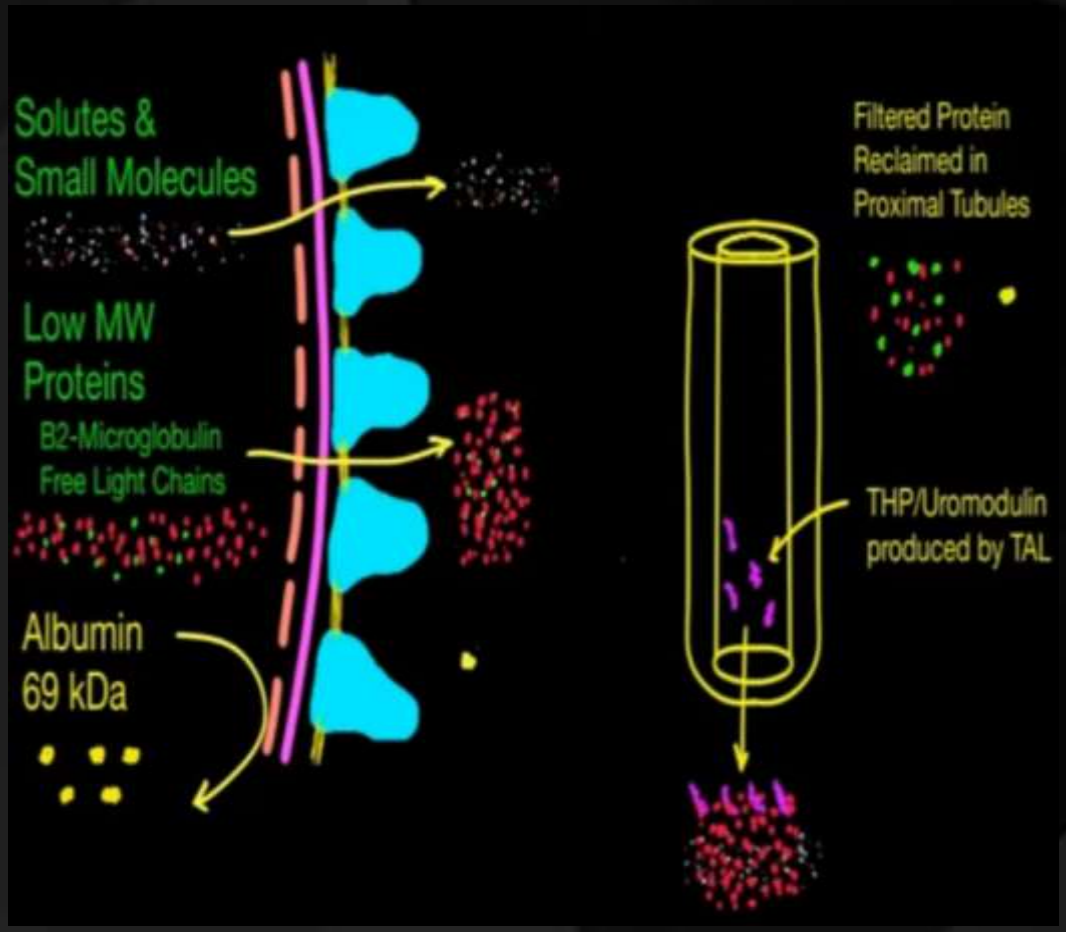
- Nephrotoxic drugs(NSAIDS,Amphotericin, aminoglycoside,Heavy metal poisoning)
- Metabolic -hyperuricemia,hypercalcaemia
- Interstitial nephritis(PPI, infections)
- Sjogren syndrome
- Hereditary:Fanconi syndrome

NEPHROTOXIC DRUGS



OVERFLOW PROTEINURIA

Marked overproduction of a particular low molecular weight protein leading to increased glomerular filtration and excretion



CAUSES :

- Multiple myeloma(light chains)
- Rhabdomyolysis (myoglobin)
- Amyloidosis
- Intravascular Hemolysis(haemoglobin)
- AML(lysozyme)

- Variant of proteinuria -**ORTHOSTATIC PROTEINURIA**

- Aka postural proteinuria

- Proteinuria of upto 1g/day in an upright position and
- Normal protein excretion in the supine position

- WHEN TO SUSPECT?

- Young and lean individuals with isolated proteinuria
- Asymptomatic
- Normal bp
- Normal RFT
- Other transient causes ruled out

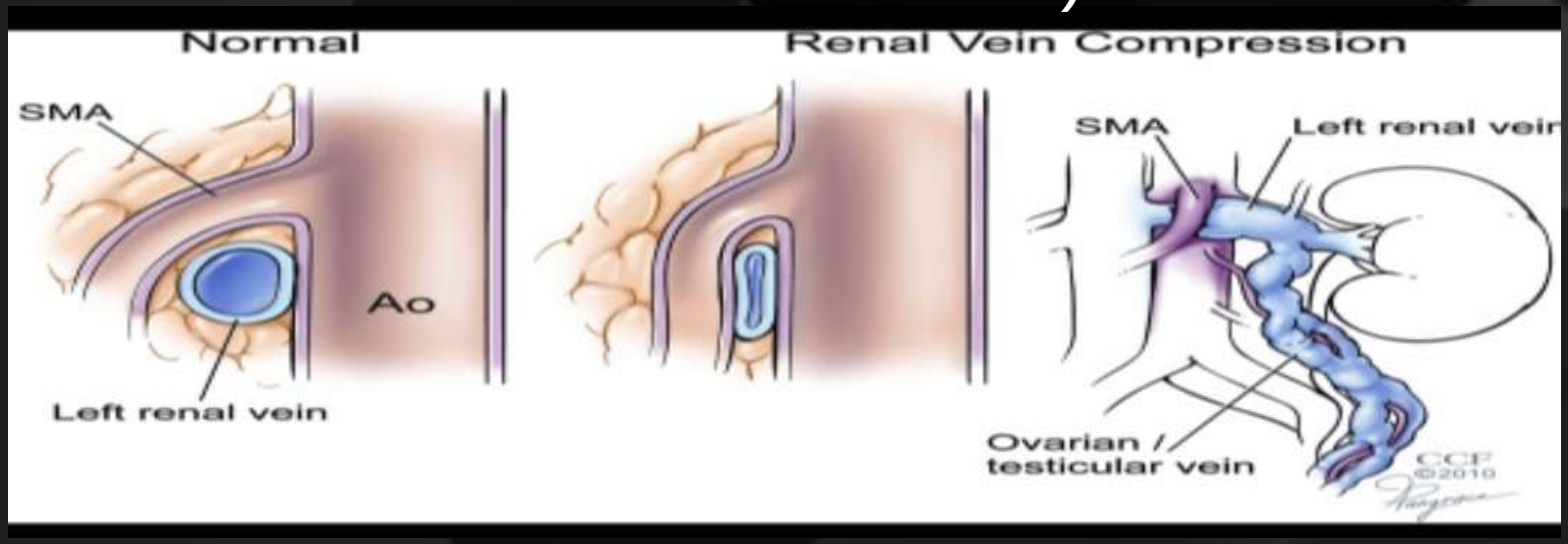
- It can be transient or even persistent.

POSSIBLE MECHANISMS

Subtle glomerular abnormalities-Thickening of the glomerular capillary wall

Exaggerated hemodynamic response - Increased efferent arteriolar resistance by ANGIOTENSIN 2

Partial obstruction of the left renal vein in the upright position (NUTCRACKER PHENOMENON)



Does every pt with + urine dipstick need evaluation?

- NO

- Asymptomatic
- Young and middle aged
- No comorbidities
- Isolated proteinuria <1g/day
- No active urine sediment
- Normal RFT
- Normal BP

- In such cases R/O TRANSIENT PROTEINURIA by repeating URINE DIPSTICK

If DIPSTICK still positive R/O ORTHOSTATIC PROTEINURIA

CLINICAL FEATURES OF PROTEINURIA

- Puffiness of face
- Pedal edema
- Abdominal distension
- Shortness of breath
- Passage of foamy urine
- Weight gain
- Hematuria
- Decreased urine output
- Fatigue
- Lack of appetite
- Flank pain

Facial puffiness

MUEHRCKE lines

Pedal edema

XANTHELASMA

IMPORTANCE OF HISTORY TAKING

Rule out any causes that lead to transient Proteinuria (Uti,fever, exercise, pregnancy)

History of HTN, DM, heart failure

HTN ,oliguria,hematuria gives clue of NEPHRITIC SYNDROME

Puffiness of face ,pedal edema ,Xanthelesma -NEPHROTIC Syndrome ?

Post pharyngitis - PSGN

H/o arthralgias, skin rashes, and mouth ulcers- Connective tissue diseases

Nephrotoxic drug history - Aminoglycosides,Pencillamine,Herbal medicines,NSAIDS, Lithium

Unexplained weight loss,Loss of appetite ,Bone pains - Malignancy

Complications of proteinuria

- Pulmonary edema due to fluid overload
- Hypovolemic crisis,AKI due to intravascular depletion ,and progressive kidney disease
- Increased risk of bacterial infections
- Increased risk of arterial and venous thrombosis, including renal vein thrombosis
- Increased risk of cardiovascular disease

TAKE HOME POINTS

- PROTEINURIA - Physiological- 150mg/day
- Isolated proteinuria <1g/day,Asymptomatic,Normal rft ,bp,No urine sediment-Transient Proteinuria
- Repeat dipstick -ve confirms transient Proteinuria
- Repeat dipstick+ ve R/o orthostatic proteinuria
- Febrile Proteinuria with UPER of>1g/day could be associated with underlying glomerular pathology

- Non isolated proteinuria,>1g/day ,symptomatic abnormal rft,High bp needs evaluation
-
- Complications of proteinuria - renal vein thrombosis, infections,Pulmonary edema, hypovolemic crisis
- . Proteinuria promotes renal damage
- . Proteinuria increases the risk of CAD,STROKE

Thank you

INVESTIGATIONS

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend initial screening of at risk individuals with a standard urine dipstick.

URINE DIPSTICK

URINE DIPSTICK

- Detects Albumin primarily
- Very specific (97%)
- Not sensitive to low levels of albumin excretion(<10 to 20 mg/dL)
- Reflects glomerular proteinuria

False positive

- In gross hematuria
- Specific antiseptics (eg, chlorhexidine, benzalkonium)
- Exposure to iodinated radiocontrast agents in contrast studies
- Alkaline urine (pH > 8)
- Urine SG ≥1.030

False negatives

- Dilute urine sample
- Low urine SG
- Tubular proteins
- Monoclonal heavy/light chains

Always Exclude conditions where mild proteinuria +

- Urinary tract infection
- Acute febrile illnesses
- Massive hematuria
- Recent strenuous exercise

Positive dipstick test

Quantitative test such as spot urine protein:creatinine (PCR) or albumin:creatinine ratio (ACR) = 24 hour urine protein quantification.

Spot Urine protein-to-creatinine ratio (UPCR) and Spot urine albumin to creatinine ratio(UACR):

Early morning urine sample can be used

- Check if creatinine excretion is nearly 1g/day

Disadvantages

- Vary throughout the day
- Large muscle mass higher creatine excretion underestimate proteinuria
- Cachectic patient lesser creatinine excretion overestimate proteinura

The accepted gold standard is

24 hour urinary protein excretion

Normal range is <150 mg/day total protein
<30 mg/day albumin

Method of collection

Early morning sample is discarded and urine is collected through out the day and night and early morning sample of next day is also collected

Disadvantages

- Frequent errors
- Impractical in children, outpatients, elderly patients

	24 h Albumin (mg/24 h)	Albumin/Creatinine Ratio (mg/g)	24 h Protein (mg/24 h)	Dipstick/Protein Reagent Strip
Normal to mildly increased albuminuria	5-10	<30	<150	Negative
Moderately increased albuminuria	30-300	30-300	150-500	Trace to 1+
Severely increased albuminuria	>300	>300	>500	1+ to 4+
Nephrotic range proteinuria	>3500	>3500	>3500	4+

CASE A
14 year old boy with fever with proteinuria 3+,no RBC ,UACR 850 with normal RFT normal albumin REST WNL

CASE B
17 year old boy with exhaustion after a marathon with proteinuria 3+ RBC 10 UACR 900 normal RFT normal albumin REST WNL

CASE C
21 year old lady with symptoms of fever and lower UTI with proteinuria 3+ RBC 40 WBC 120 UACR 1000 normal RFT normal albumin REST WNL

ANSWER : TRANSIENT PROTEINURIA

Repeat the tests after 1 to 2 weeks

Dipstick becomes negative and proteinuria resolving with normal RFT

CASE D

18 year old asymptomatic male got admitted as he has proteinuria in his medical check up
NON HTN/NON DM
NO SIGNIFICANT FAMILY HISTORY
HB - 12
TLC- 11000 with N - 89
USG ABDOMEN - normal URINE C/S - negative
URINE ANALYSIS - prot 3+,RBC nil wbc nil
CREAT - 0.8 UREA - 60 LFT - normal
UPER - 900 mg/day

DIAGNOSIS : ORTHOSTATIC PROTEINURIA

SPLIT URINE Testing

Early morning first void sample is discarded
Collect urine sample in one container during the day time
FOLLOWING MORNING collect the first morning urine sample in night jug

Day sample will be abnormal
night sample will be normal

Normal UPCR < 0.15 in first morning urine specimen
Elevated in second upright spot urine specimen

CASE E

21 year old female with C/O

Fever on and off for one year on multiple antibiotics and ATT
Pedal edema for 15 days ,hairloss, loss of weight,arthralgia
vitals stable
systemic examination normal

HB 12,TLC 11000 with N 89%
CXR normal,USG ABD normal URINE ,C/S negative
prot ; 3+ RBC 40 WBC 10 RBC CASTS +
CREAT 1.2 UREA 60

UPER : 2000 mg/day

DIAGNOSIS : PERSISTENT PROTEINURIA

Repeat tests after 1 to 2 weeks

Urine microscopy

Systemic symptoms

DIFFERENTIAL DIAGNOSIS

- DIABETIC NEPHROPATHY
- NEPHROTIC SYNDROME
- NEPHRITIC SYNDROME
- AMYLOIDOSIS
- LUPUS NEPHRITIS PLUS VASCULITIS
- TOXEMIA OF PREGNANCY
- DRUG INDUCED - D PENCILLAMINE,GOLD
- PERSISTENT ISOLATED PROTEINURIA

DIABETIC - Sugars,fundoscopy

NEPHROTIC - Generalised edema,lipid profile,LFT

NEPHRITIC - HTN,Facial puffiness,oliguria

LUPUS - oral ulcers , photosensitivity, joint pains, rash

H/O of drug usage any blood transfusions,sexual history

URINE MICROSCOPY

- Red blood cell casts/Dysmorphic red blood cells - Glomerular disease/IgA nephropathy
- Neutrophils - UTI , Urine contamination by genital secretions
- Eosinophils - GN, prostatitis, chronic pyelonephritis, urinary schistosomiasis, and cholesterol embolism.
- OVAL FAT BODIES /FATTY CASTS - Nephrotic syndrome(Maltese cross)
- Microhematuria may occur in membranous nephropathy ,FSGS

LABAROTARY STUDIES

CBP with ESR
Anemia and Raised ESR - LUPUS AND OTHER VASCULITIS

Serum creatinine, albumin, cholesterol (see HDL cholesterol and LDL cholesterol), and blood glucose determinations

Screening for infections such as human immunodeficiency virus, hepatitis B and C, and syphilis.

Urinary protein immune electrophoresis

In the absence of an obvious cause of proteinuria the workup should also include measurements of

- ✓ Antinuclear antibody
- ✓ Anti Ds DNA
- ✓ Antineutrophil cytoplasmic antibodies (C-ANCA and P-ANCA)
- ✓ Complement levels

to evaluate for rheumatologic diseases (eg, systemic lupus erythematosus, Wegener granulomatosis, Goodpasture syndrome, cryoglobulinemia), lymphoproliferative diseases, and solid organ cancers.

Renal ultrasonography

- Normally 9 to 12 cm in length in adults
- It also helps in planning for biopsy
- Helps in ruling out structural causes

Indications for Renal Biopsy

- Nephrotic Syndrome
- Acute Kidney Injury
- Systemic Disease With Renal Dysfunction (DM,LUPUS NEPHRITIS,VIRUSES RELATED)
- Non-Nephrotic Proteinuria
- Isolated Microscopic Hematuria
- Unexplained Chronic Kidney Disease
- Familial Renal Disease
- Renal Transplant Dysfunction

Indications for Renal Biopsy

Nephrotic Syndrome

- In prepubertal children, indicated only if clinical features atypical of minimal change disease present

✓ Microhematuria

✓ Reduced serum complement levels

✓ Renal impairment

✓ Failure to respond to corticosteroids.

Acute Kidney Injury

Biopsy indicated in AKI accompanied by an

- ✓ Active urine sediment
- ✓ Suspected drug-induced interstitial nephritis
- ✓ Infection-induced acute interstitial nephritis

DIABETES MELLITUS

Biopsy not indicated if

- Isolated proteinuria
- diabetes of long duration
- Evidence of other microvascular complications.

Renal biopsy should be performed if the presentation is

- ✓ Proteinuria with glomerular hematuria (acanthocytes)
- ✓ Absence of retinopathy or neuropathy
- ✓ Onset of proteinuria less than 5 years from documented onset of diabetes
- ✓ Rapid change in renal function or renal disease of acute onset

LUPUS NEPHRITIS

The 2012 ACR guidelines for lupus nephritis recommend kidney biopsy for all cases of active, previously untreated lupus nephritis

Kidney biopsy is used to confirm the presence of lupus nephritis; to aid in classification of systemic lupus erythematosus (SLE) nephritis

Class I - Minimal mesangial
Class II - Mesangial proliferative
Class III - Focal proliferative
Class IV - Diffuse proliferative
Class V - Membranous
Class VI - Advanced sclerosing

Unexplained Chronic Kidney Disease

Renal biopsy can done in the patient with unexplained chronic renal impairment and normal-sized kidneys

However, if both kidneys are small (<9 cm on ultrasound),the risks of biopsy are increased and the diagnostic information may be limited by extensive glomerulosclerosis and tubulointerstitial fibrosis.

Immunofluorescence studies may be informative in this setting

Glomerular IgA deposition is identified by immunoflorescence technique despite advanced structural damage.

Repeat Renal Biopsy

- LUPUS NEPHRITIS

- MISDIAGNOSED FSGS as
Corticosteroid-resistant MCD
Corticosteroid dependent MCD
Frequently relapsing MCD

- Crescentic GN FOR the most appropriate next line of therapy.

Contraindications to Renal Biopsy

Kidney Status

Multiple cysts
Solitary kidney
Acute pyelonephritis
Perinephric abscess
Renal neoplasm

Patient Status

Uncontrolled bleeding diathesis
Uncontrolled blood pressure
Uremia
Obesity
Uncooperative patient

TAKE HOME POINTS

URINE DIPSTICK POSITIVE

RULE OUT
Highly alkaline urine (pH > 7)
Concentrated urine
Gross hematuria
Mucus, semen, or leukocytes
Iodinated contrast agent
Contamination with chlorhexidine or benzalkonium

LOOK FOR RENAL OR SYSTEMIC DISEASES

History: systemic disease (DM, Malignancy, SLE)

Physical exam: rashes, ederna, palpable purpura, stigmata of auto-immune disease, etc

Vitals: hypertensive, febrile

Urine sediment exam: dysmorphic RBCs, casts (RBCs, WBCs), lipiduria

Labs: CBC, creatinine, GFR,sugars,viral serology ,serological studies

ABSENT

PRESENT

ISOLATED PROTEINURIA

NON ISOLATED PROTEINURIA

ISOLATED PROTEINURIA
normal urine sediment
normal kidney function
no significant history

REPEAT DIPSTICK

YES

PERSISTENT ISOLATED PROTEINURIA

RULE OUT ORTHOSTATIC PROTEINURIA

NO

TRANSIENT PROTEINURIA
fever,stress,exercise,obesity,infections,CHF

PERSISTENT PROTEINURIA

QUANTIFY BY UPCR
CREATININE AND GFR
RENAL ULTRASOUND to rule out structural causes
URINE PROTEIN ELECTROPHORESIS

NEPHROTIC RANGE PROTEINURIA

KIDNEY BIOPSY

NON NEPHROTIC RANGE PROTEINURIA

IMMUNE ELECTROPHORESIS

ALBUMIN

KIDNEY BIOPSY

Non albumin

MYELOMA/ TUBULOINTERSTITIAL EVALU

NON ISOLATED PROTEINURIA

- HISTORY
- PHYSICAL EXAMINATION
- LABARATORY STUDIES
- SEROLOGICAL TESTS
- URINE MICROSCOPY
- RENAL BIOPSY FOR DEFINITIVE DIAGNOSIS