

**In the name of GOD**

**Approach to  
proteinuria**

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IUMS

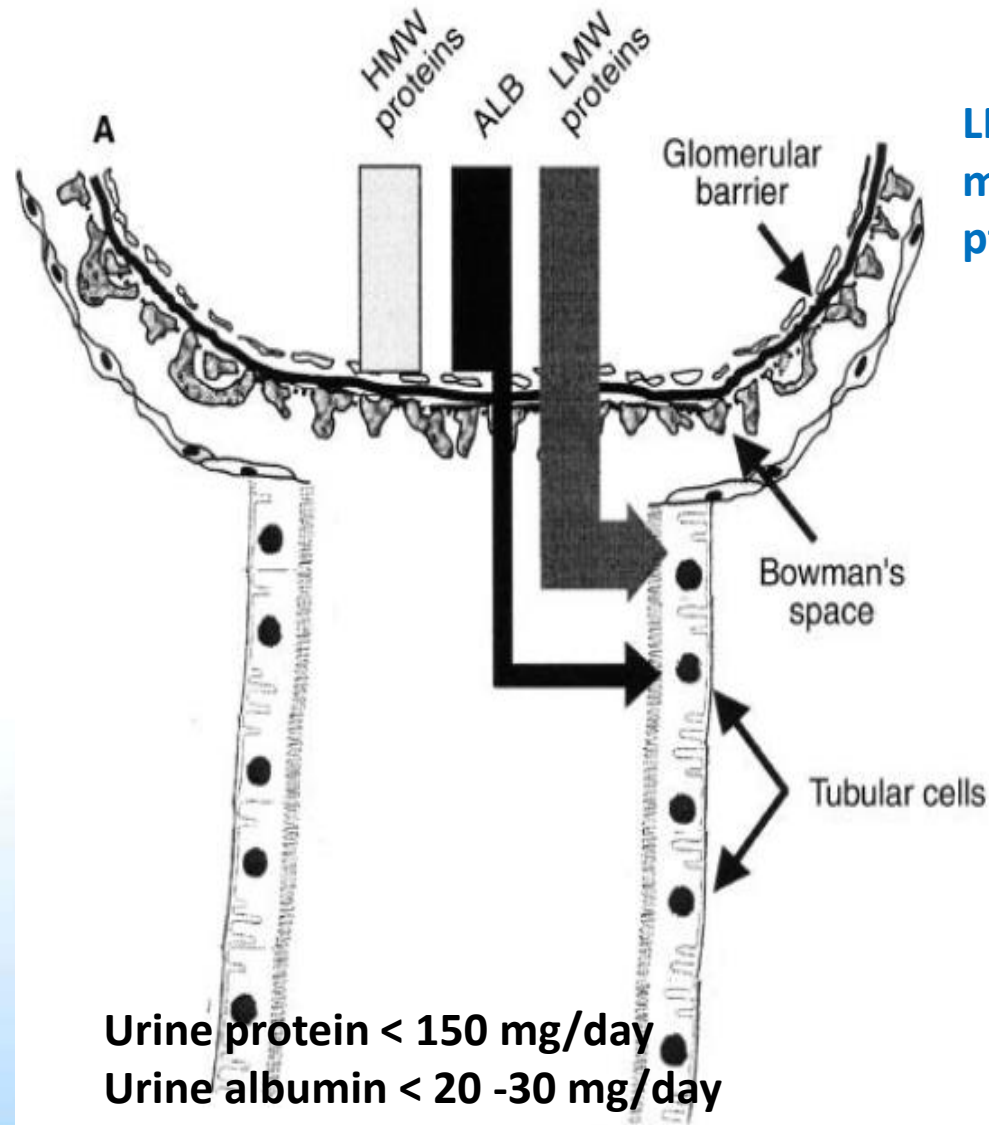
## Normal urine protein excretion

- less than 150 mg/24 h for adults
- <140 mg/m<sup>2</sup> for children
- **It is composed of:**
  - 40 to 60 mg of Tamm-Horsfall, IgA
  - 20 to 30 mg of albumin
  - 10 to 20 mg of low-molecular-weight proteins

## NORMAL PHYSIOLOGY

- In humans, on the basis of a GFR of 100 mL/min, 180 L of primary urine is produced per day
- contains about 10 kg of protein
- 0.01% or 1 g of protein passes through the glomerular filtration barrier into the filtrate

HMW plasma  
proteins(Alb,globulin)



LMW proteins ( $\alpha_2$   
microglobulin, apoproteins, peptide hormones, enzymes)

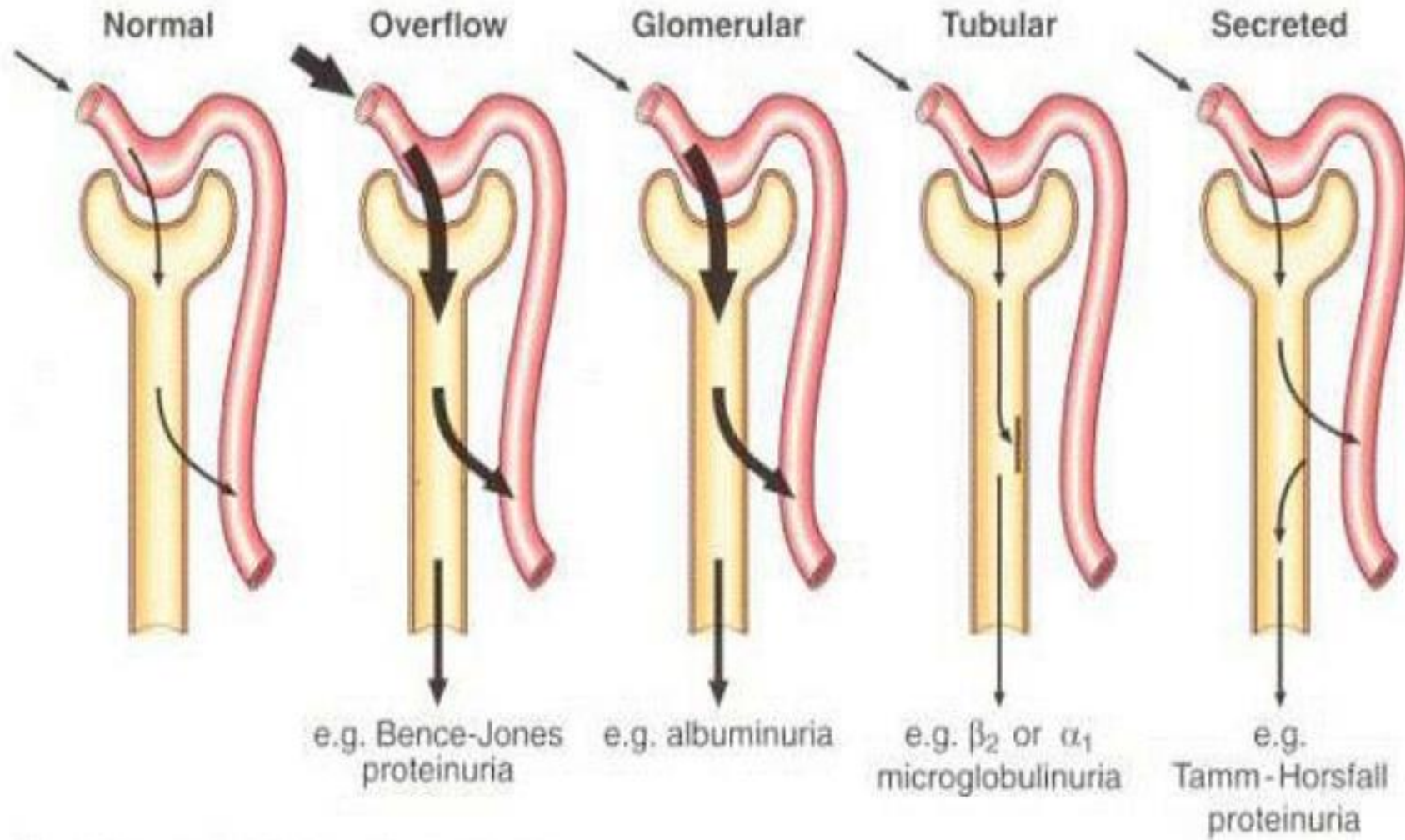
Tamm–  
Horsfall protein,  
IgA, urokinase

## **AbNL amount of protein in the urine:**

- DISRUPTION OF THE CAPILLARY WALL BARRIER
- TUBULAR DAMAGE OR DYSFUNCTION
- NL OR AbNL PLASMA PROTEIN PRODUCTION IN INCREASED AMOUNT

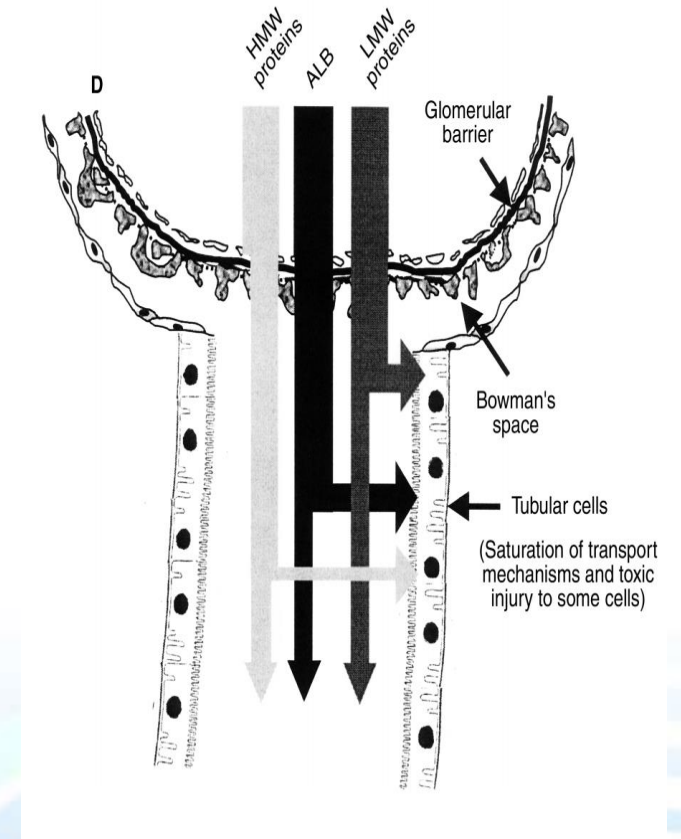


## Pathological proteinuria



## Glomerular proteinuria

- increased filtration of macromolecules such as Alb
- sensitive marker for glomerular disease
- proteinuria associated with
  - diabetic nephropathy
  - other glomerular diseases
  - benign causes, such as orthostatic proteinuria



# Tubular proteinuria

- Tubular damage or dysfunction
- higher amounts of mostly LMW proteins beta2-microglobulin, ig light chains, retinol-binding protein, and polypeptides in the urine
- due to a variety of tubulointerstitial diseases or even some primary glomerular diseases
- Classic causes of tubular proteinuria in isolation are Fanconi syndrome and Dent disease



# Overflow proteinuria

- Increased excretion of LMW proteins
- marked overproduction of a particular protein
- **almost always** due to ig light chains in MM
- Myoglobin, free hemoglobin, lysozyme

The increased excretion of ig light chains (or Bence Jones proteins) in:

➤ **overflow proteinuria in MM**

monoclonal and potentially nephrotoxic

➤ **tubular proteinuria**

mild, polyclonal (both kappa and lambda), not injurious to the kidney

.

## Postrenal proteinuria

- Inflammation in the urinary tract, urinary tract infection, nephrolithiasis or tumors of the urinary tract
- Small amounts
- usually nonalbumin IgG or IgA
- Leukocytes are also commonly present in the urine sediment

## Amounts of proteinuria

- In normal individuals, LMW proteins and small amounts of albumin are filtered by the glomerulus
- Most of the filtered albumin is almost completely reabsorbed in proximal tubule
- The net result is the normal daily protein excretion of less than 150 mg (usually 40 to 80 mg)
- approximately 4 to 7 mg is intact, immunoreactive albumin



- normal rate of Alb is approximately 4 to 7 mg/day in healthy young adults
- increases with age and with an increase in body weight
- Persistent Alb excretion between 30 and 300 mg/day :moderately increased albuminuria
- Albumin excretion above 300 mg/day :overt proteinuria or severely increased albuminuria
- Even within the normal range, higher amounts of albuminuria are associated with an increased risk of cardiovascular disease

# DETECTION AND MEASUREMENT OF TOTAL URINARY PROTEIN EXCRETION

- Two semi quantitative methods
  - standard urine dipstick
  - precipitation of urine proteins with sulfosalicylic acid (SSA)
- Neither method is quantitative
- if AbNL proteinuria is suggested by either technique, should be quantified using a timed urine collection

## Standard urine dipstick

- primarily detects albumin
- relatively insensitive to non-albumin proteins
- a positive dipstick usually reflects glomerular proteinuria
- very specific but not sensitive to low levels of Alb
- The lower limit of detection is a urine Alb concentration of approximately 10 to 20 mg/dL

## Albumin Reagent Strip

- is based on the effect of Alb on a buffer (tetrabromophenol blue)
- causes a change in pH proportional to the concentration of the Alb
- The pad changes color, from pale green to green and blue
- is expressed on a scale from 0 to ++++





## Standard urinary dipstick

Negative

Trace :15 - 30 mg/dL

1+ : 30 - 100 mg/dL

2+ : 100 - 300 mg/dL

3+ : 300 - 1000 mg/dL

4+ : >1000 **mg/dL**

## **False positive urine dipstick results**

- After the use of iodinated radiocontrast agents
- highly alkaline urine (pH greater than 8)
- gross hematuria and a urocrit
- specific antiseptics (chlorhexidine, benzalkonium)

## Sulfosalicylic acid test

- detects **all** proteins in the urine at a sensitivity of 5 to 10 mg/dL
- A significantly positive SSA test in conjunction with a negative dipstick, usually indicates the presence of non-albumin proteins in the urine, most often ig light chains

## false positive results

- iodinated radiocontrast agents
- in the presence of penicillins, sulfisoxazole
- gross hematuria

# Quantitative measurement

## 24-hour urine collection

- The **gold standard** for measurement of protein excretion
- **The major limitations :**
  - cumbersome for patients
  - often collected incorrectly
- The adequacy of the collection can be estimated by quantifying the 24-hour urine creatinine



## UPCR and UACR

- measuring the urine pr-to-cr ratio (UPCR) in a spot first- or second-morning urine sample or occasionally the urine Alb-to-cr ratio (UACR) is used to estimate 24-hour proteinuria
- Usually, the urine pr concentration in a spot sample is measured in **mg/dL** and is divided by the urine cr concentration (**mg/dl**), yielding a number that estimates the 24-hour pr excretion in **grams per day**
- If **SI units** are used, the value for the UPCR or UACR in units of mg of pr per g of cr is **divided by 8.8**
- As an example, a UACR of **30 mg/g** cr is equivalent to **3.4 mg/mmol** cr

## Limitations of the UPCR and UACR

- The UPCR is easy for patients and providers
- the correlation with daily pr excretion is reasonably good on the population level
- **two major limitations** of using random spot urine samples to quantify proteinuria:
  - UPCR and UACR are heavily influenced by the urine cr concentration and therefore by the total daily cr production
  - Urine pr excretion can vary throughout the day (especially resulting from exercise and posture) and from day to day

Source: [https://www.kidney-international.org/article/S0025-3709\(16\)00090-0](https://www.kidney-international.org/article/S0025-3709(16)00090-0)

## Influence of the urine creatinine

- The UPCR is useful on the population level because the average 24-hour urine cr excretion for the population is assumed to be approximately 1000 mg/day per 1.73 m
- the accuracy of the ratio is diminished if cr excretion is either markedly higher or lower than the average population value of 1000 mg/day
- In individuals with **large muscle mass**, in whom cr excretion may be much higher than 1000 mg/day, the UPCR (or UACR) will **underestimate** proteinuria
- In patient with **small muscle mass**, in whom cr excretion may be much lower than 1000 mg/day, the UPCR (or UACR) will **overestimate** proteinuria

## **Estimated albumin excretion rate (eAER) and estimated protein excretion rate ( ePER)**

- more accurately predict the 24-hour albumin and protein excretion
- eAER can be calculated by multiplying the spot UACR by the expected 24-hour creatinine generation
- ePER can be calculated by multiplying the spot UPCR by the expected 24-hour creatinine generation
- A 24-hour urine collection should be obtained during the initial evaluation, measuring the excretion of both protein and creatinine



- If the initial 24-hour urine collection seems complete, The ePER or eAER on this 24-hour specimen can be related to the total amount of proteinuria or albuminuria and also compared with a random spot ePER or eAER
- Random specimens can subsequently be used to monitor the degree of proteinuria as long as muscle mass appears stable
- If follow-up measurements of the ePER or eAER suggest that a clinically important change in protein excretion has occurred, a 24-hour urine collection should be obtained to verify the change in proteinuria before therapy is altered

## Diagnostic Evaluation of Proteinuria

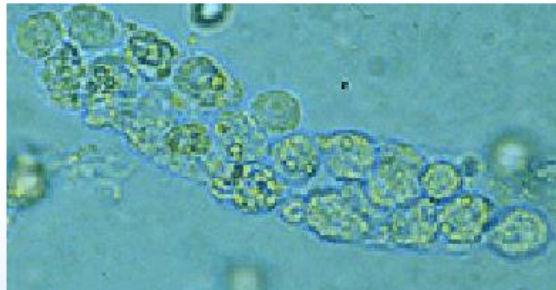
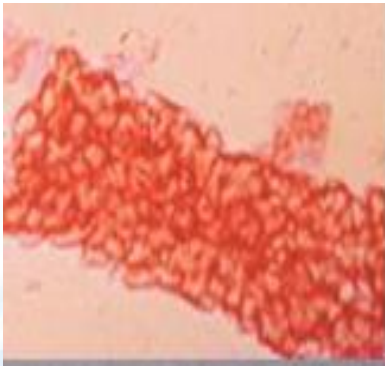
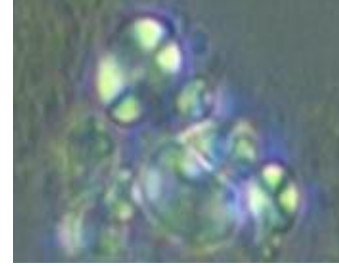
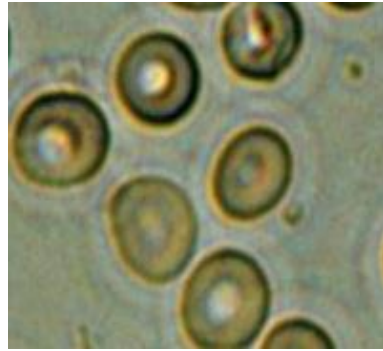
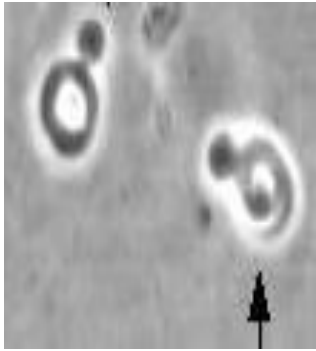
- **When proteinuria is found on a dipstick urinalysis:**
- the first important step is to rule out causes for a false positive test
- careful history, physical exam and vitals, labs and urine studies
- Depending on these results, radiologic studies, serology and renal biopsy

- urinary sediment should be examined microscopically
- active urine sediment :presence of >5 RBCs and >5 WBCs per HPF and/or the presence of cellular casts
- Dysmorphic erythrocytes indicating glomerular disease
- Gross hematuria will cause proteinuria on dipstick urinalysis

## Interpretation of Findings on Microscopic Examination of Urine

<i>MICROSCOPIC FINDING</i>	<i>PATHOLOGIC PROCESS</i>
Fatty casts, free fat or oval fat bodies	Nephrotic range proteinuria (> 3.5 g per 24 hours)
Leukocytes, leukocyte casts with bacteria	Urinary tract infection
Leukocytes, leukocyte casts without bacteria	Renal interstitial disease
Normal-shaped erythrocytes	Suggestive of lower urinary tract lesion
Dysmorphic erythrocytes	Suggestive of upper urinary tract lesion
Erythrocyte casts	Glomerular disease
Waxy, granular or cellular casts	Advanced chronic renal disease
<u>Eosinophiluria*</u>	Suggestive of drug-induced acute interstitial nephritis
Hyaline casts	No renal disease; present with dehydration and with diuretic therapy







- If the results of microscopic urinalysis are **unremarkable** ,dipstick urinalysis shows **trace to 2+** protein:
- the dipstick test should be **repeated** on a morning specimen at **least twice** during the **next month**
- when proteinuria **3+ or 4+** is found on a dipstick urinalysis, work-up should proceed to a **quantitative evaluation** of a specimen
- A patient with **isolated proteinuria** (normal urine sediment, normal kidney function) who has no obvious etiology identified by the history and physical exam should be evaluated for **transient proteinuria** and **orthostatic proteinuria**

## TRANSIENT PROTEINURIA

- Relatively common
- Age < 18 years: 8 –12 % ,> 18 years: 4%
- No hematuria and/or reduced eGFR
- Usually < 1g /day, but can go up to > 2g / day
- Resolves when a causative factor is no long present
- Marked exercise, febrile illness such as, UTI, emotional stress, most acute illness, decompensated CHF
- not associated with increased morbidity and mortality
- specific follow-up is not indicated

## orthostatic proteinuria

- relatively common in adolescents (2 - 5%)
- uncommon in adults over the age of 30 years
- increased protein excretion in the upright position
- Total protein excretion is generally less than 1 g/day but may exceed 3.5 g/day in selected patients
- kidney function and proteinuria should be followed yearly to monitor

## PERSISTENT PROTEINURIA

- a detailed history and physical examination should be performed
- looking for systemic diseases with renal involvement
- A medication history is particularly important
- A 24-hour urine protein measurement or a UPr/Cr ratio on a random urine specimen should be obtained

- adult with proteinuria of **more than 2 g per 24 hours** requires aggressive work-up
- If the cr clearance is normal and patient has a clear diagnosis such as diabetes or decompensated CHF, the underlying medical condition can be treated with close follow-up of proteinuria and renal function
- A patient with proteinuria of **more than 2 g per 24 hours** and a **decreased cr clearance** or an **unclear cause** should have further testing performed



## Selected Investigations to Be Considered in Proteinuria

TEST	INTERPRETATION OF FINDING
Antinuclear antibody	Elevated in systemic lupus erythematosus
<u>Antistreptolysin O titer</u>	Elevated after streptococcal glomerulonephritis
Complement C3 and C4	Levels are low in <u>glomerulonephritides</u>
Erythrocyte sedimentation rate	If normal, helps to rule out inflammatory and infectious causes
Fasting blood glucose	Elevated in diabetes mellitus
Hemoglobin, hematocrit, or both	Low in chronic renal failure that impairs hematopoiesis

TEST	INTERPRETATION OF FINDING
HIV, VDRL, and hepatitis serologic tests	HIV, hepatitis B and C, and syphilis have been associated with glomerular proteinuria
Serum albumin and lipid levels	Albumin level decreased and cholesterol level increased in nephrotic syndrome
Serum electrolytes ( $\text{Na}^+$ , $\text{K}^+$ , $\text{Cl}^-$ , $\text{HCO}_3^-$ , $\text{Ca}^{2+}$ and $\text{PO}_4^{2-}$ )	Provide a screening examination for any abnormalities following renal disease
Serum and urine protein electrophoresis	Results are abnormal in multiple myeloma
Serum urate	In addition to stones, elevated urate can cause <u>tubulointerstitial</u> disease
Renal ultrasonography	Provides evidence of structural renal disease
Chest radiograph	Can provide evidence of systemic disease (e.g., sarcoidosis)

## Role of kidney biopsy

- all patients with proteinuria of **more than 3.5 g/day**
- **non-nephrotic proteinuria** is associated with an **active urine sediment** or **decreased GFR**
- In patients with **isolated non-nephrotic proteinuria** with subsequent monitoring, the **degree of proteinuria increases** and persists above 1 g/day  
or if the patient develops **new glomerular hematuria, hypertension**, or a **reduction in estimated GFR**
- patients with **isolated non nephrotic proteinuria** to diagnose a **suspected systemic process** if the diagnosis cannot be made reliably any other way

- The level of persistent isolated non-nephrotic proteinuria that should be evaluated by kidney biopsy has not been well defined
  - most nephrologists perform a biopsy in patients with non-nephrotic proteinuria of 2 g/day or more
  - Some would perform a biopsy for persistent proteinuria 1-2 g/day if there are clinical and/or serologic clues suggesting a systemic disease that might be detected by kidney biopsy
- or if there is a possible hereditary disease, such as Fabry disease



## Summary:

### Types of proteinuria

- Glomerular proteinuria
  - Tubular proteinuria
  - Overflow proteinuria
  - Post-renal proteinuria
- 
- **24-hour urine collection** :The gold standard for measurement of protein excretion



- A patient with isolated proteinuria should be evaluated for transient proteinuria and orthostatic proteinuria
- A kidney biopsy should be done in all patients with proteinuria of more than 3.5 g/day
- The level of persistent isolated non-nephrotic proteinuria that should be evaluated by kidney biopsy has not been well defined



*THANK  
YOU*