"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all."
William Osler

Medicine

430

Nephrotic Syndrome

By: Hadeel AlSajjan

Nephrotic Syndrome

Definition:

- Nephrotic syndrome is not a specific glomerular disease but a constellation of clinical findings that result from increased glomerular permeability to the plasma proteins.
- Nephrotic syndrome is a kidney disease with proteinuria, hypoalbuminemia, and edema.
- The glomerular derangements that occur with nephrosis can develop as a primary disorder or secondary to changes caused by systemic diseases such as diabetes mellitus, amyloidosis, and SLE.

The nephrotic syndrome is characterized by

- Massive proteinuria (>3.5 g/day)
- Lipiduria (*e.g.,* free fat, oval bodies, fatty casts)
- Hypoalbuminemia (<3 g/dL), Generalized edema
- Hyperlipidemia (cholesterol >300 mg/dL).

Pathophysiology:

Protienurea

- The initiating event in the development of nephrosis is a derangement in the glomerular membrane that causes increased permeability to plasma proteins.
- The glomerular membrane acts as a size and charge barrier through which the glomerular filtrate must pass.
- Any increased permeability allows protein to escape from the plasma into the glomerular filtrate

Edema

- Generalized edema, which is a hallmark of nephrosis, results from salt and water retention and a loss of serum albumin below that needed to maintain the colloid osmotic pressure of the vascular compartment.
- The sodium and water retention appears to be due to several factors, including a compensatory increase in aldosterone, stimulation of the sympathetic nervous system, and a reduction in secretion of natriuretic factors.
- Initially, the edema presents in dependent parts of the body such as the lower extremities, but becomes more generalized as the disease progresses.

Hyperlipidemia

- The hyperlipidemia that occurs in persons with nephrosis is characterized by elevated levels of triglycerides and low-density lipoproteins (LDLs). Levels of high-density lipoproteins (HDLs) usually are normal.
- It is thought that these abnormalities are related, at least in part, to increased synthesis of lipoproteins in the liver secondary to a compensatory increase in albumin production
- Because of the elevated LDL levels, persons with nephrotic syndrome are at increased risk for development of atherosclerosis.

- Hypertension related to fluid retention and reduced kidney function may occur.
- Decreased immunoglobulin count (which are proteins) leads to an increase susceptibility to infections.
- Hypercoagulability → Venous thrombosis and pulmonary embolism are well-known complications of the nephrotic syndrome. Hypercoagulability in these cases appears to derive from urinary loss of anticoagulant proteins, such as antithrombin III and plasminogen, along with the simultaneous increase in clotting factors, especially factors I, VII, VIII, and X.

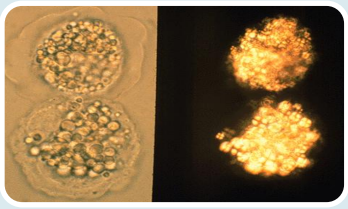
Muehrcke's nails

Paired white transverse lines

Occures in Hypoalbuminemia (e.g. Nephrotic Syndrome)

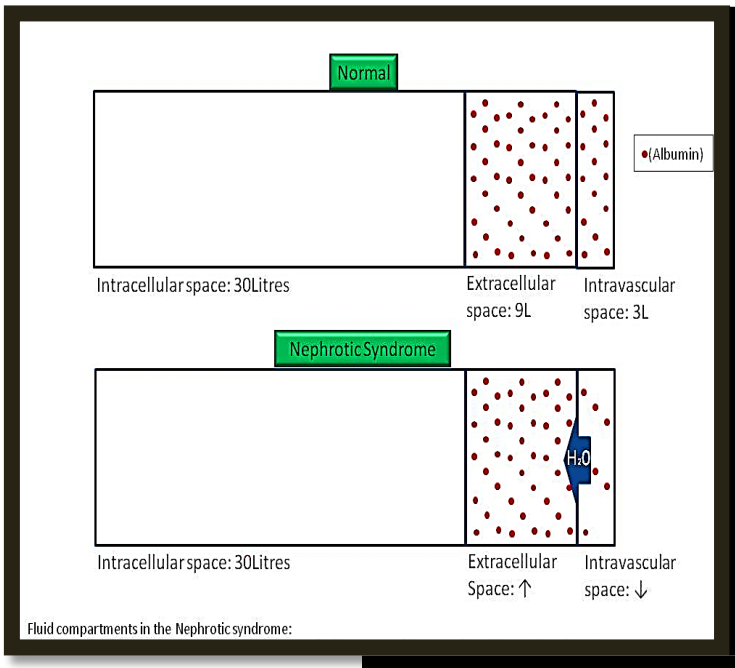
Leuconychia

Occures in Hypoalbuminemia (e.g. Nephrotic Syndrome)

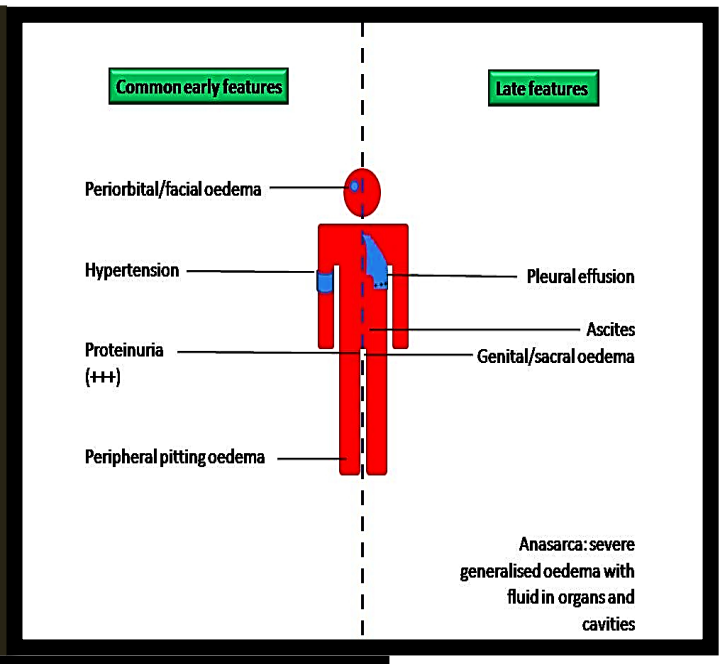


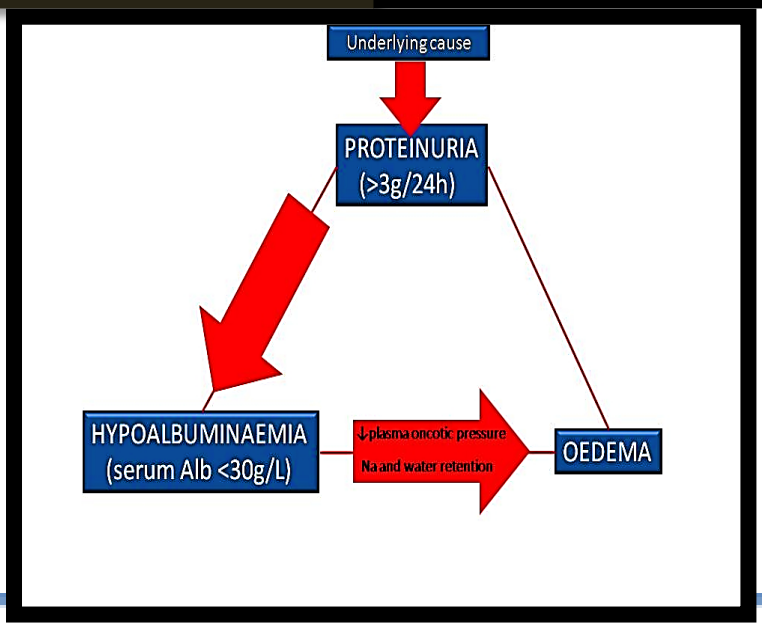
Lipidurea

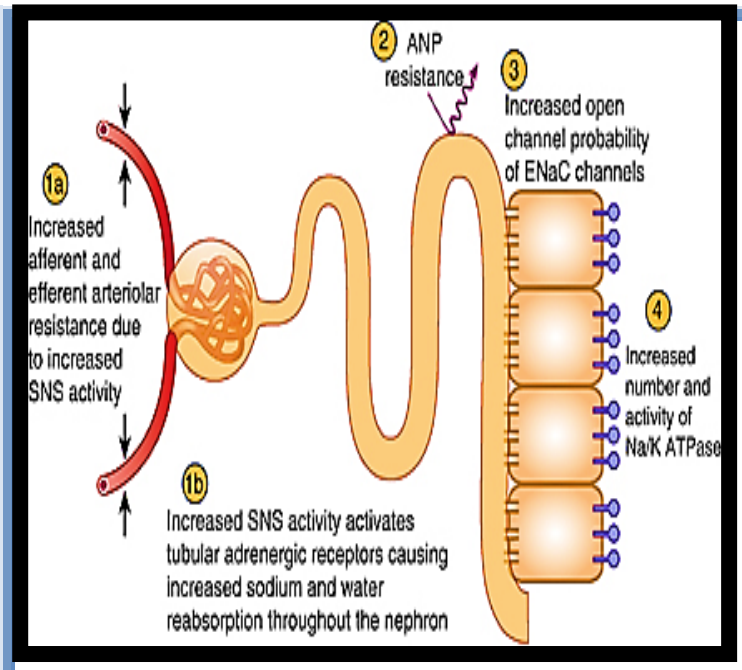
Fatty casts in urine

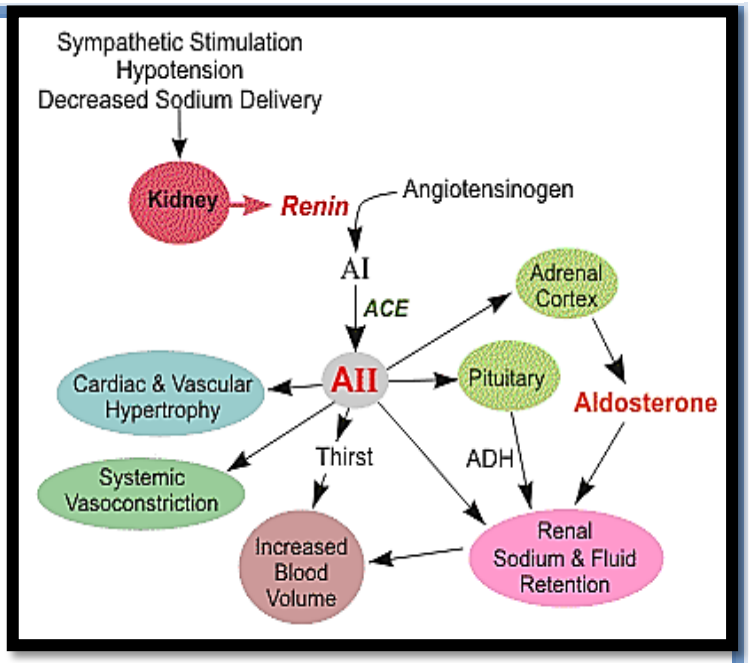


Fluid compartments in the Nephrotic syndrome:









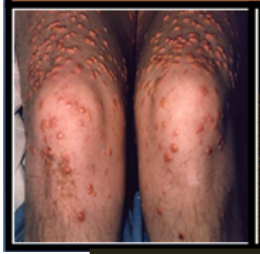
Nephrotic Syndrome*

proteinuria* → reduced albumin* → reduced oncotic pressure

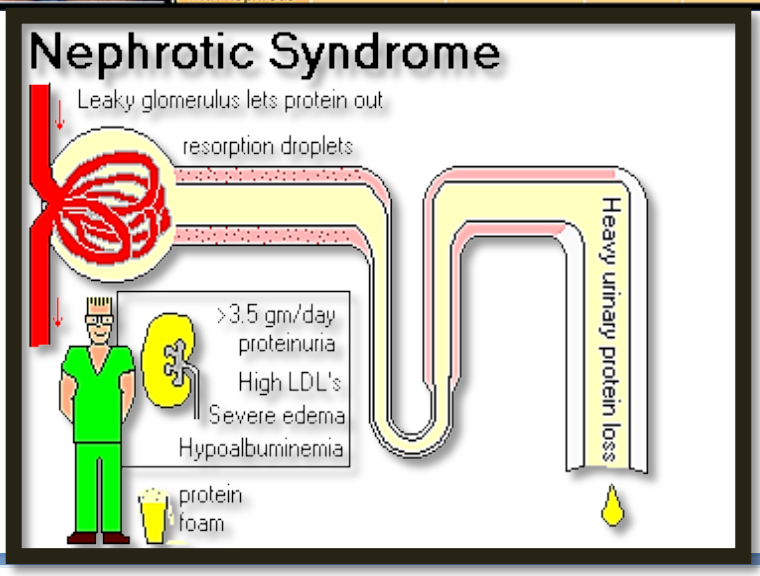
reduced blood volume ← edema*

renin/angiotensin/aldosterone & ADH

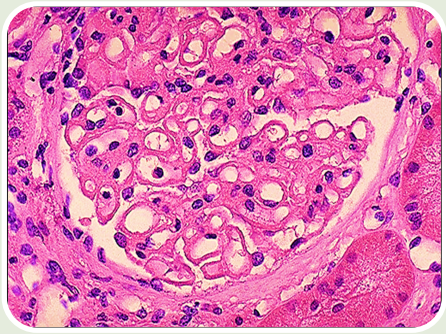
liver increases production of albumin and lipoprotein carriers of TG and cholesterol*



	Total Cholesterol >240 mg/dL	LDL Cholesterol >130 mg/dL	HDL <35 mg/dL	Triglycerides >200 mg/dL
General population	20%	40%	15%	15%
Chronic kidney disease with nephrotic	60%	85%	50%	60%

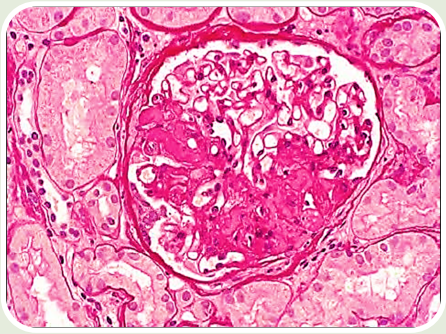


Primary Glomerulopathies:



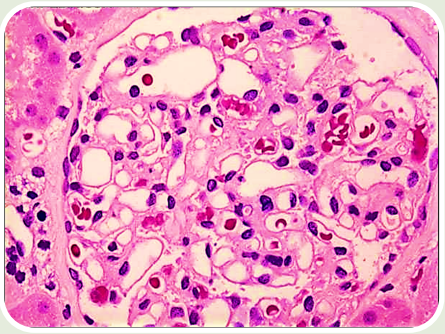
Membranous Glomerulonephritis

- Membranous glomerulonephritis is the most common cause of primary nephrosis in adults, most commonly in their sixth or seventh decade.
- (> 50 years of age)
- The disorder is caused by diffuse thickening of the GBM due to deposition of immune complexes.
- More common in American-White people



Focal Segmental Glomerulosclerosis

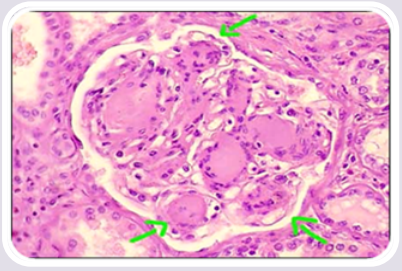
- Focal segmental glomerulosclerosis is characterized by sclerosis (i.e., increased collagen deposition) of some but not all glomeruli.
- In the affected glomeruli, only a portion of the glomerular tuft is involved.
- (Between 10-50 years of age)
- More common in African Americans



Minimal Change Disease

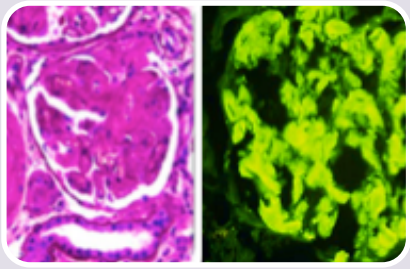
- Minimal change disease is characterized by diffuse loss (through fusion) of the foot processes from the epithelial layer of the glomerular membrane.
- The peak incidence is between 2 amd 6 years of age (< 10 years of age)
- Shows no change on light microscopy.

Secondary Glomerulopathies: (Systemic causes)



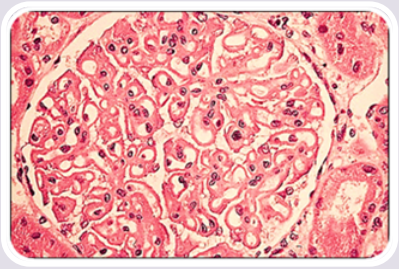
Diabetic Glomerulosclerosis (Diabetic Nephropaty)

- Most common secondary glomerulopathy
- Diffuse glomerulosclerosis



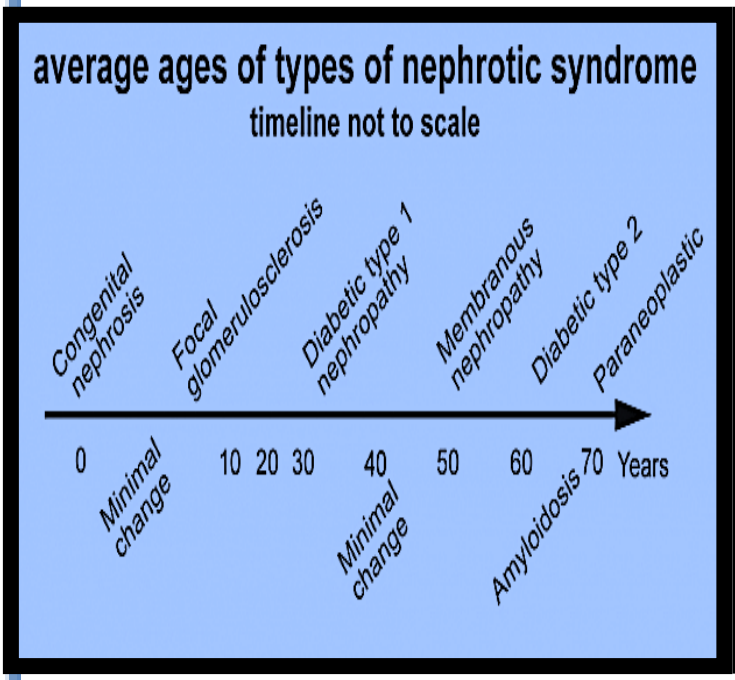
Amyloidosis (Due to Multiple Myeloma)

- Dipossition of protiens in the glomeruli
- Second most common systemic cause
- Differentiated from Diabetic Glomerulosclerosis through special stains
- Mostly found in elderly males



Lupus Nephritis caused by Systemic Lupus Erythematosus (SLE)

- Double-line appearing membrane (Membrane thickening)
- Mostly found in young females

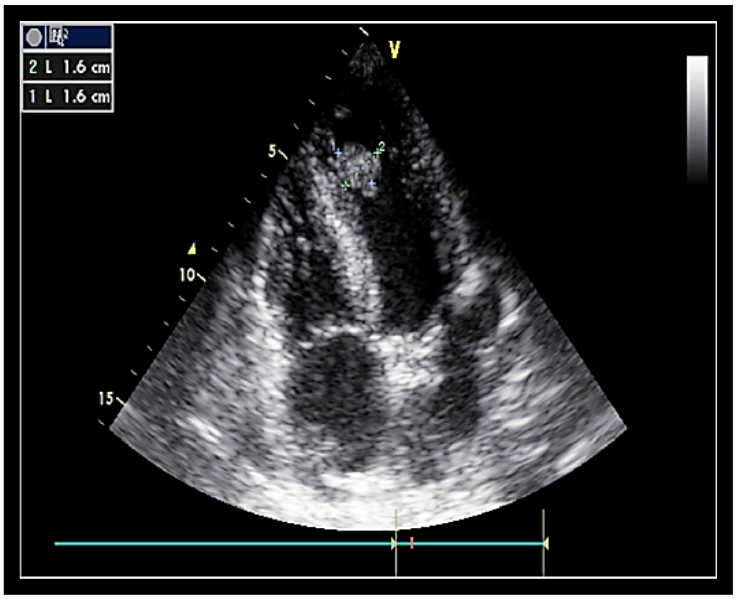


Nephrotic Syndrome Recap

- Adults main causes
  - Diabetes, SLE, amyloidosis, etc. (40%)
  - Membranous glomerulonephritis (20%)
  - All forms of proliferative glomerulonephritis (15%)
  - Minimal change glomerulonephritis (10%)
  - Focal glomerulosclerosis (10%)
  - Membranoproliferative glomerulonephritis (5%)
- Children main causes
  - Minimal change glomerulonephritis (60%)
  - Focal glomerulosclerosis (10%)
  - All forms of proliferative glomerulonephritis (10%)
  - Membranoproliferative glomerulonephritis (10%)
  - Membranous glomerulonephritis (5%)
  - Secondary to systemic disorder (5%)

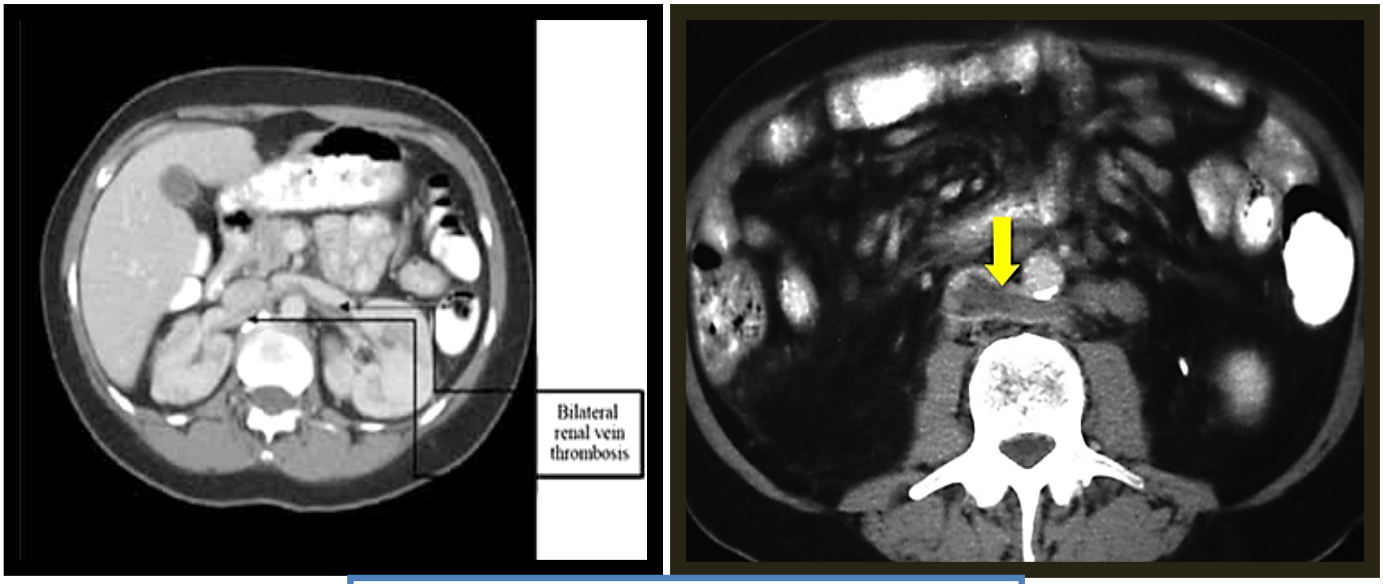
PRIMARY CAUSES (80%)	FREQUENCY	AGE	BIOPSY FEATURES	Rx
Minimal Change Glomerularnephritis	• Most common cause in children • Cause in 25% adults	Children adolescents	Normal glomeruli under light microsopy	High dose steroids (good response) (does not progress to ESRF)
Focal segmental Glomerulosclerosis (FSGS)	• Cause in 33% of patients	Children adolescents	Scarring in glomeruli (focal)	High dose steroids (Mixed response) (recurs after Tx)
Membranous Nephropathy	• most common cause in adults	30-50y/o most affected	Thickened GBM Ig containing deposits on the GBM	• Steroids •Immunosuppressive therapy (1/3remit, 1/3remain, 1/3 develop ESRF)
Mesangiocapillary Glomerulonephritis	• Cause in 5% of patients	All ages	Split GBM aka "Tram-tracking"	Little evidence, steroids may help in children (50% develop ESRF)

Complications of Nephrotic Syndrome: (Life threatening complications)

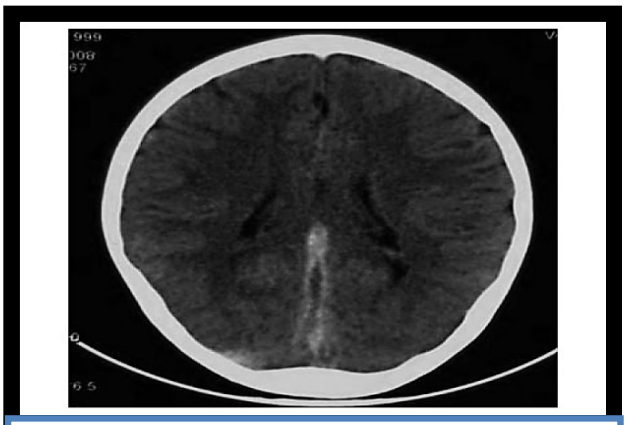


Thrombosis is commonest complication of Nephrotic Syndrome
DVT is the most common type of thrombosis

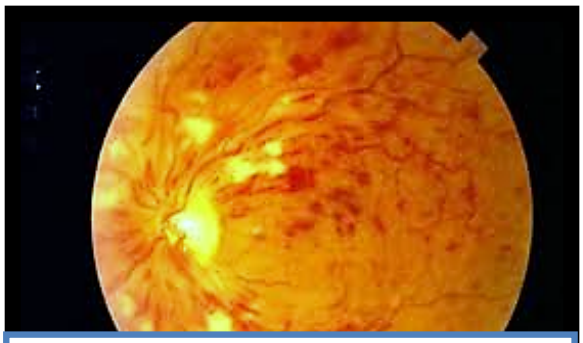
- Image shows thrombus in the left atrium of the heart
- Due to excessive liver production of proteins (including coagulation factors) as a compensatory mechanism, leading to a hypercoagulability state, leading to thrombus formation



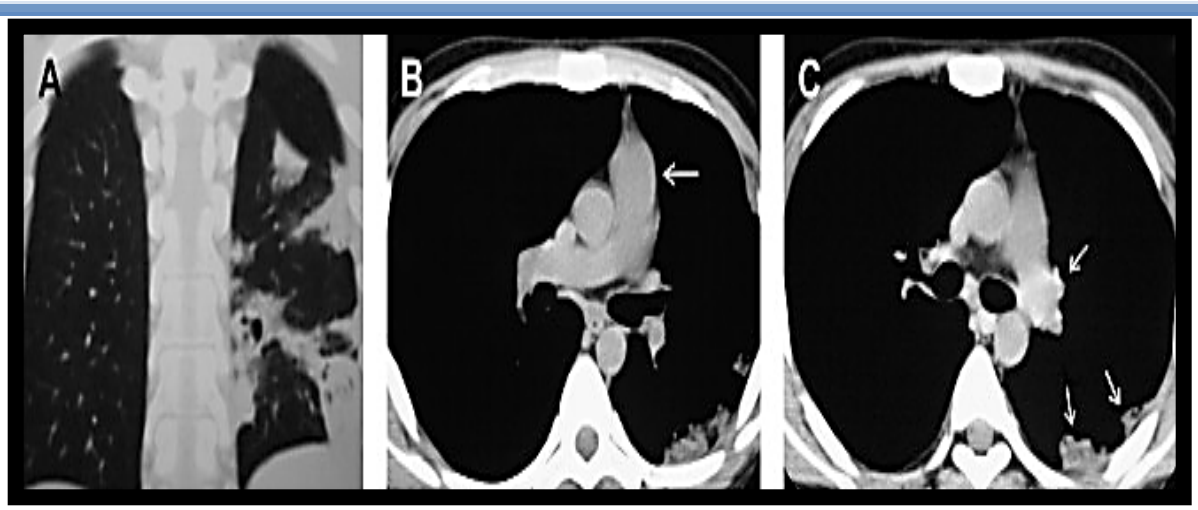
Bilateral Renal Vein Thrombosis



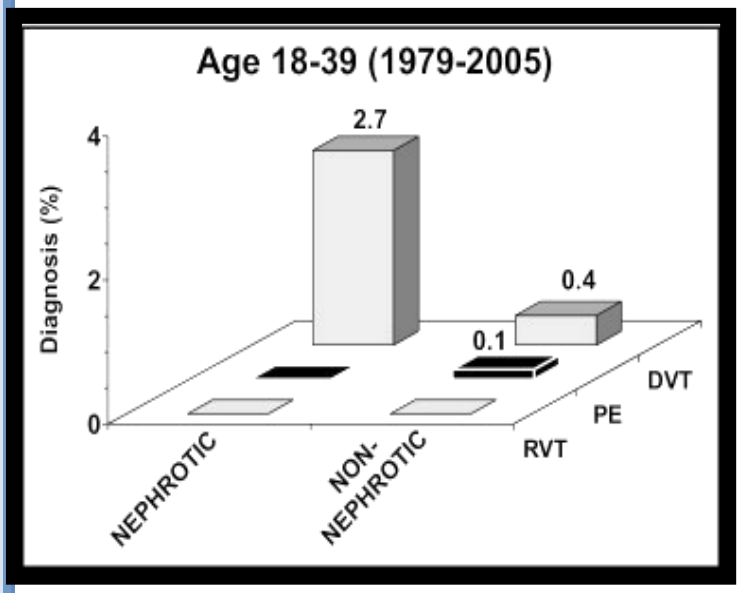
Superior Sinus Thrombosis

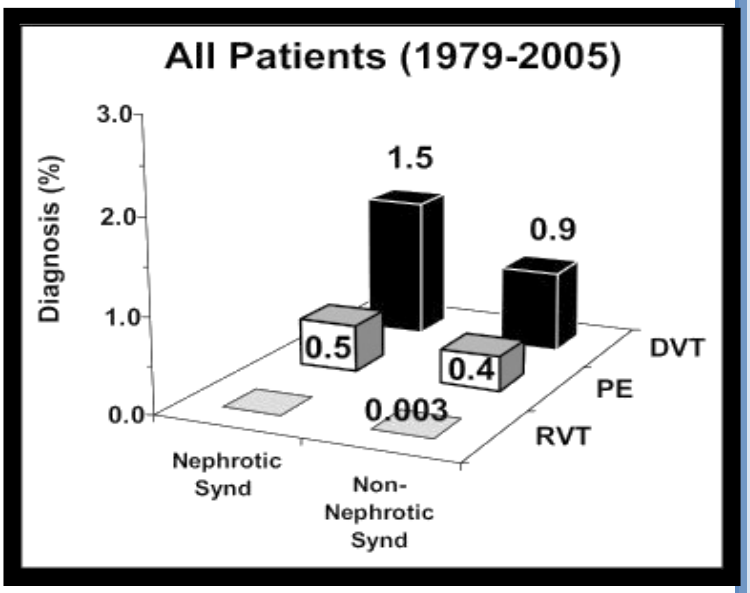


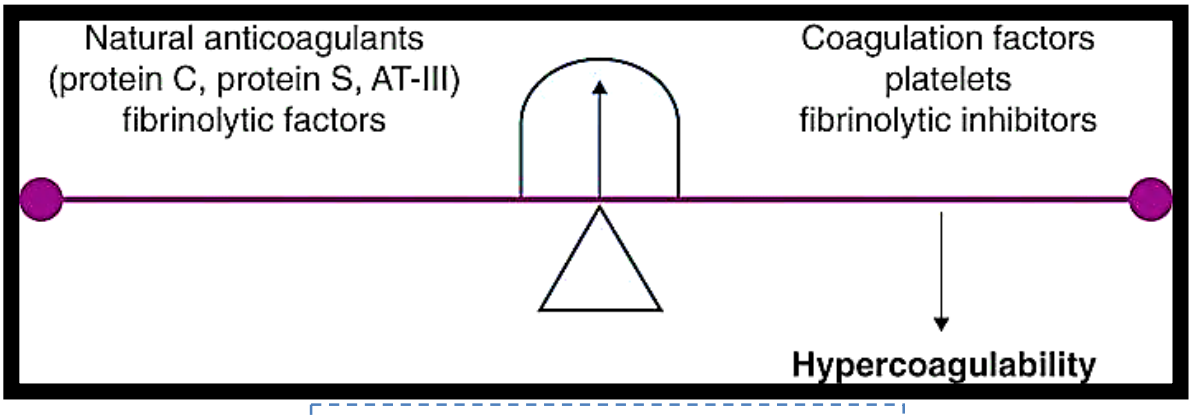
Central Retinal Vein Thrombosis (The hemorrhage seen is due to the hypertension caused by the occlusion)



Massive Pulmonary Embolism



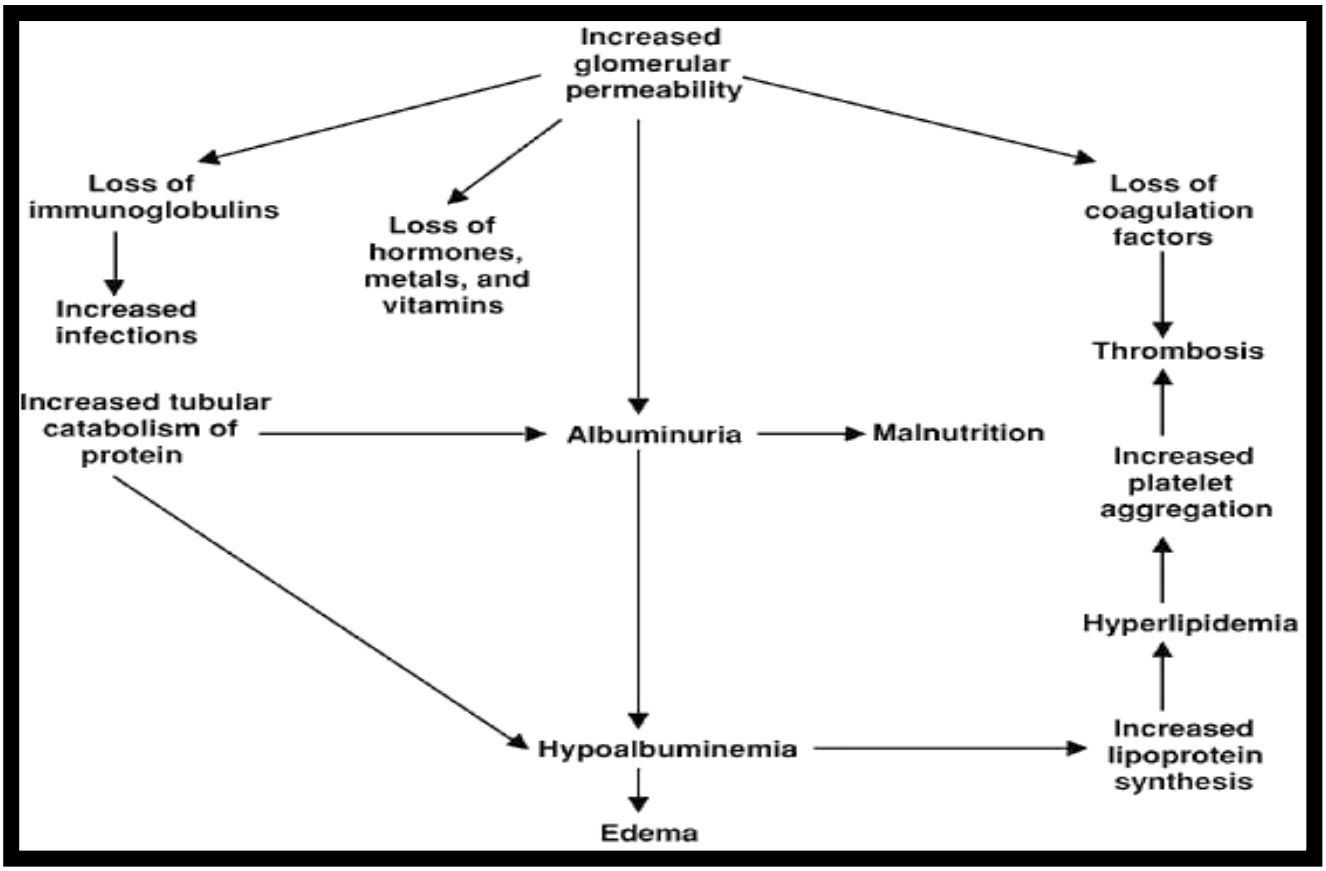




Mechanism of Thrombus Formation
(An increase in the factors on the right leads to Hypercoagulability)

Case report author	Age years/ Sex	Onset of nephrotic syndrome prior to thrombosis	Site of arterial thrombosis	Renal histology	Coagulation factors ↑	Coagulation factors ↓	Steroids/ diuretics use prior to thrombosis	Albumin gm/dl)	Other factors	Treatment: Anti coagulation	Treatment: Thrombolytics/ thrombosis	Out come
Ibrahim Fahal[8]	27/M	18 months	Bilteral profunda femoris	Mesangio proliferative GN	Fibrinogen	Anti thrombin III	Diuretics	1.8	Smoking	Yes	No	Good
	47/F	6 months	Right iliac	Mesangio proliferative GN	Fibrinogen	Anti thrombin III	Diuretics + steroids	2.7	Smoking	Yes	Thrombec-tomy	Good
Misha Witz[9]	44/A1	Diagnosed at the same time	Left subclavian and brachial	Not biopsied	Fibrinogen	Anti thrombin III and Protien S	No	1.5	Smoking	Heparin followed by warfarin	Thromboem-bolectomy	Good
JD Pandian[10]	42/A4	11 years	Right internal carotid and MCA	Minimal change disease	Not done	Not done	No	1.5	Smoking and hyper tension	No	No	Poor
Motohiro Nishimura[11]	39/A1	Diagnosed at the same time	Right femoral	Minimal change disease	Fibrinogen	Anti thrombin III	No	1.5	No	Heparin followed by warfarin	Thrombolytic therapy followed by thrombectomy	Good
Ghulam Malik[12]	23/F	2 years	Left ventricle and brachial	FSGS	Fibrinogen	Anti thrombin III	Diuretics		No	Heparin followed by warfarin	No	Good

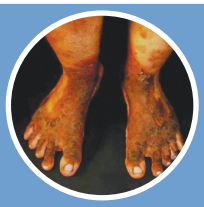
MCA = Middle cerebral artery; GN = Glomerulonephritis



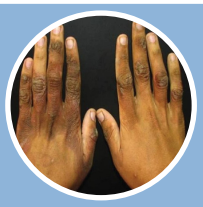
Two main causes of death in Nephrotic Syndrome:

- Infections
- Thrombosis

Other complications: (Less serious complications)



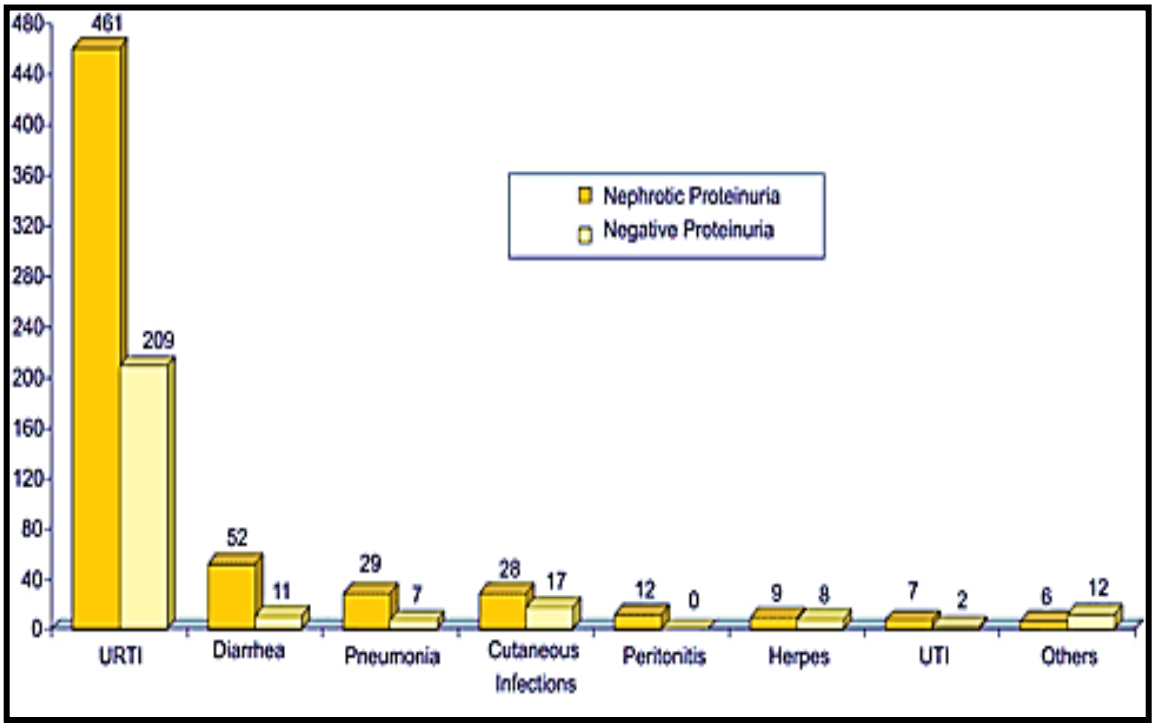
Zinc Deficiency



Zinc Deficiency

Edema (Swollen Face)
Acitis

- URTI
- Diarrhea
- Pneumonia
- Cutaneous Infections
- Peritonitis
- Herpes
- UTI
- Others

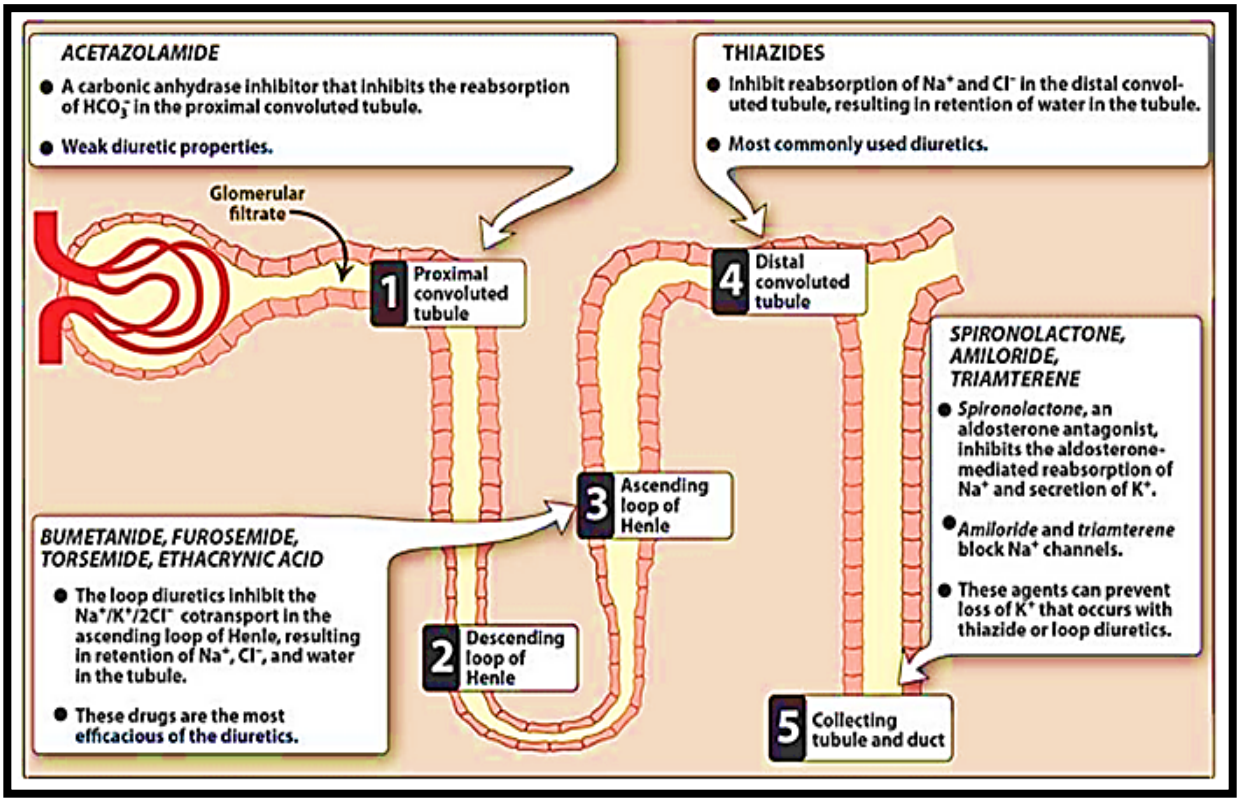


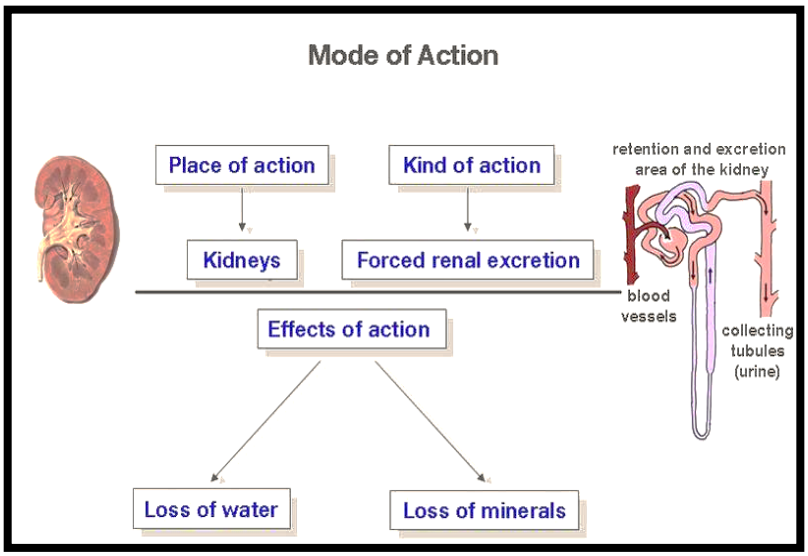
Management: (Nonspecific treatment)

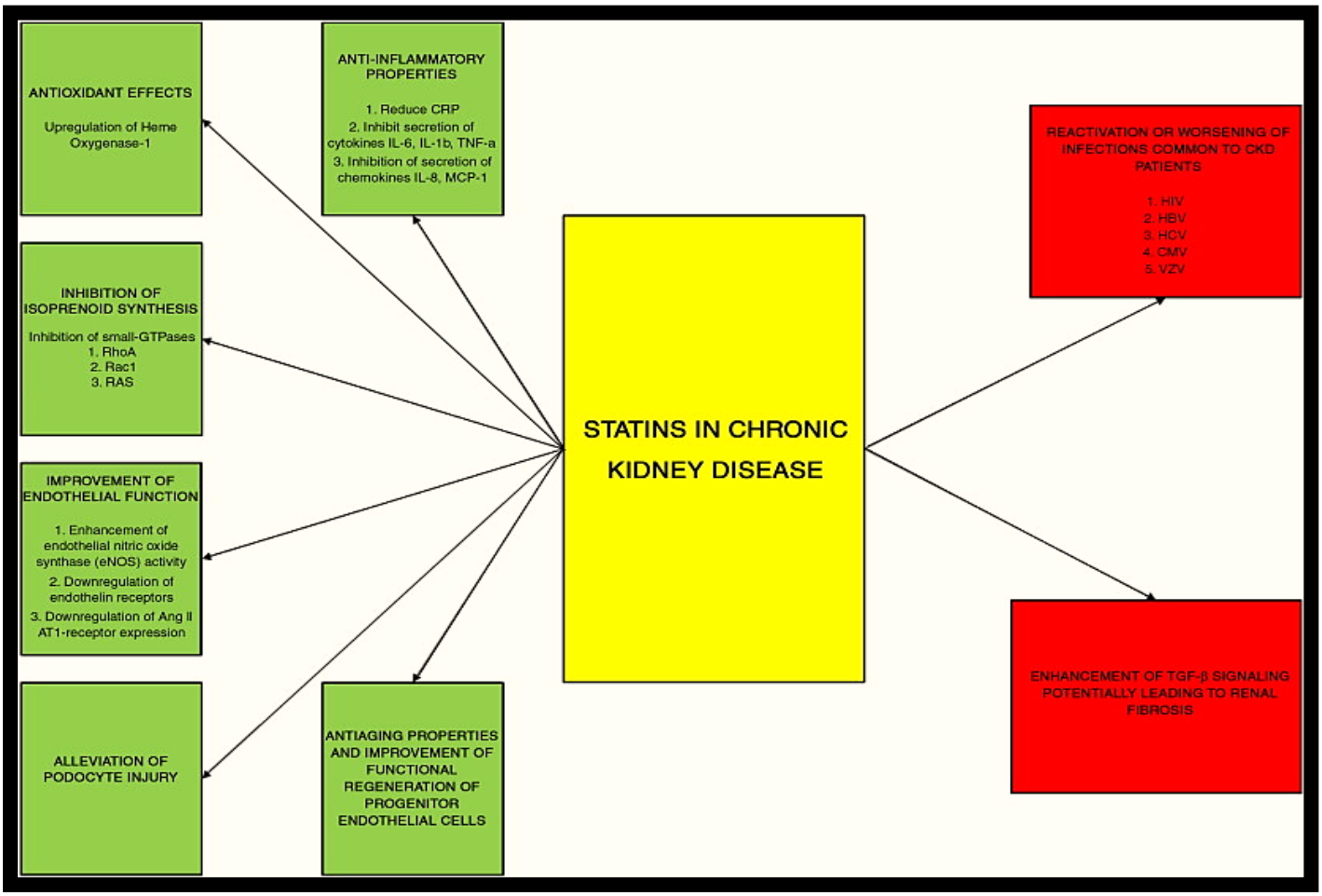
- Eating less salt
- Diuretics
  - Acetazolamide (Proximal tubule diuretic)
  - Bumetanide, Furosemide… (Loop diuretics)
    - (Most commonly used, very potent)
  - Thiazides (Distal tubule diuretic)
  - Spironolactone (Collecting tubule and duct diuretic)
    - (An important diuretic in Nephrotic Syndrome)
- Angeotensin 2 Receptor Blockers (Treats Edema) (Improves the function of podocytes, thus reducing proteinuria)
  - Losartan
- Statins (In addition to treating Hyperlipidemia, they Improve the glomerular filtration barrier)
- ACE Inhibitors
  - Captopril
  - Lisinopril
  - Enalapril

*In Secondary Glomerulonephropathies we give the treatment above in addition to treating the underlying cause.

Diuretics







References:

- Pathophysiology – Concepts of Altered Health States (7th edition)
- Medscape