Chronic Kidney Disease

By

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Pharm D

- ✓ ***Chronic kidney disease is characterized by a progressive deterioration in kidney function ultimately leading to irreversible structural damage to existing nephrons.***

- ✓ ***Progressive loss of function occurring over several months to years, and is characterized by the gradual replacement of normal kidney architecture with interstitial fibrosis.***

Stages of CKD

From National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease

Stage	*Damage*	*GFR ml/min/1.73m^2*
1	*Kidney damage with normal GFR*	*> /=90*
2	*Kidney damage with mild decrease in GFR*	*60–89*
3	*Moderate decrease in GFR*	*30–59*
4	*Severe decrease in GFR*	*15–29*
5	*Kidney failure*	*<15*

Etiology

Susceptibility factors

Advanced age

Reduced kidney mass & low birth weight

Family history

Systemic inflammation

Dyslipidemia

Initiation factors

Diabetes mellitus (44%),

Hypertension (27%),

Chronic glomerulonephritis (8%)

Progression factors

Glycemia

Hypertension

Proteinuria

smoking

obesity

Pathophysiology

The key elements of this pathway are:

(a) Loss of nephron mass

(b) Glomerular capillary hypertension

(c) Proteinuria

Glomerular Hyperfiltration and Intraglomerular Hypertension

Exposure to initiation factor

Loss of nephron mass

Progressive loss of nephron function

Adaptive changes in remaining nephrons to increase single nephron eGFR

Prolonged elevation of glomerular capillary pressure and increased glomerular plasma flow

Intraglomerular hypertension

Glomerular injury

Impairs the size-selective function of the glomerular permeability Barrier

Proteinuria

Direct cellular damage

(Albumin, transferrin, complement factors, immunoglobulins, cytokines, and angiotensin II are toxic to kidney tubular cells.)

Secretion of proinflammatory mediators

Renal fibrosis and Scarring (sclerosis)

Sclerosis may involve entire nephron

DM associated CKD

Hyperglycemia leads to a nonenzymatic reaction between sugar and protein.

Formation of advanced glycation end products (AGEs)

Complexes accumulation

AGEs cause expansion of the mesangium, damage to the glomerular basement membrane, cytokine release.

Glomerulosclerosis

Hypertension associated CKD

a) Intraglomerular hypertension and hyperfiltration

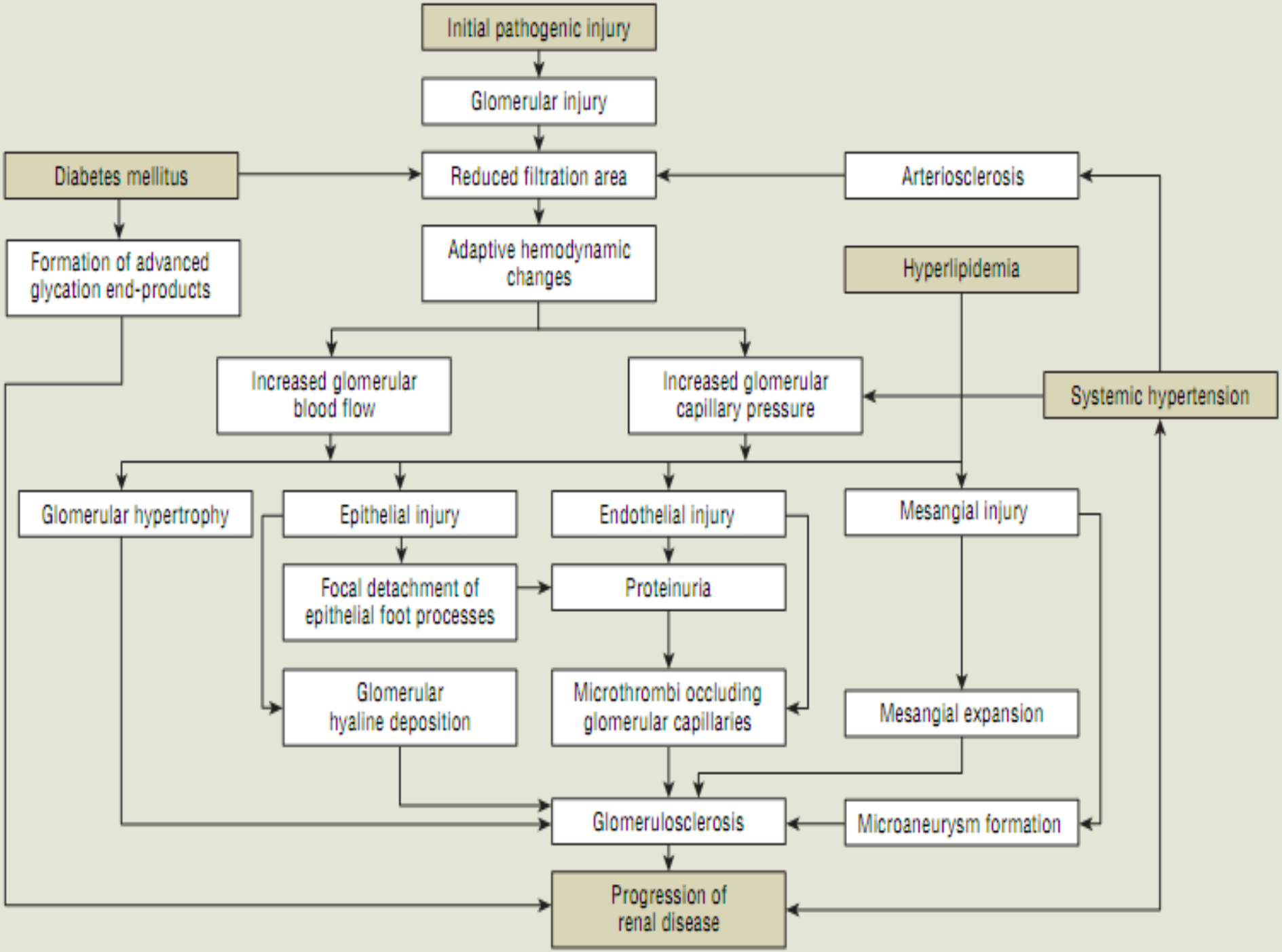
b) Arteriosclerosis (Nephron loss through ischemic mechanisms)

Dyslipidemia associated CKD

Oxidation and deposition of lipoproteins in the glomerulus and the mesangial cells

Synthesis of inflammatory cytokines, vasoactive substances, and macrophage chemotactic factors.

Glomerular scarring.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Glomerular hypertrophy
Epithelial injury
Endothelial injury
Mesangial injury
Focal detachment of epithelial foot processes
Proteinuria
Glomerular hyaline deposition
Microthrombi occluding glomerular capillaries
Mesangial expansion
Glomerulosclerosis
Microaneurysm formation
Progression of renal disease

Clinical presentation

Symptoms

- ***Symptoms are generally absent in stages 1 and 2.***
- ***Minimum during stages 3 and 4***

General symptoms associated with stages 1 to 4 include

- ✓ ***Edema***
- ✓ ***Shortness of breath***
- ✓ ***Palpitations***
- ✓ ***Cramping***
- ✓ ***Muscle pain***
- ✓ ***Depression***
- ✓ ***Anxiety***
- ✓ ***Fatigue***
- ✓ ***Sexual dysfunction.***

Consequences of CKD

Anemia

- ***Kidneys secrete 90% of erythropoietin, which is necessary for erythropoiesis***

- ***CKD ⇨ erythropoietin deficiency ⇨ Anemia***

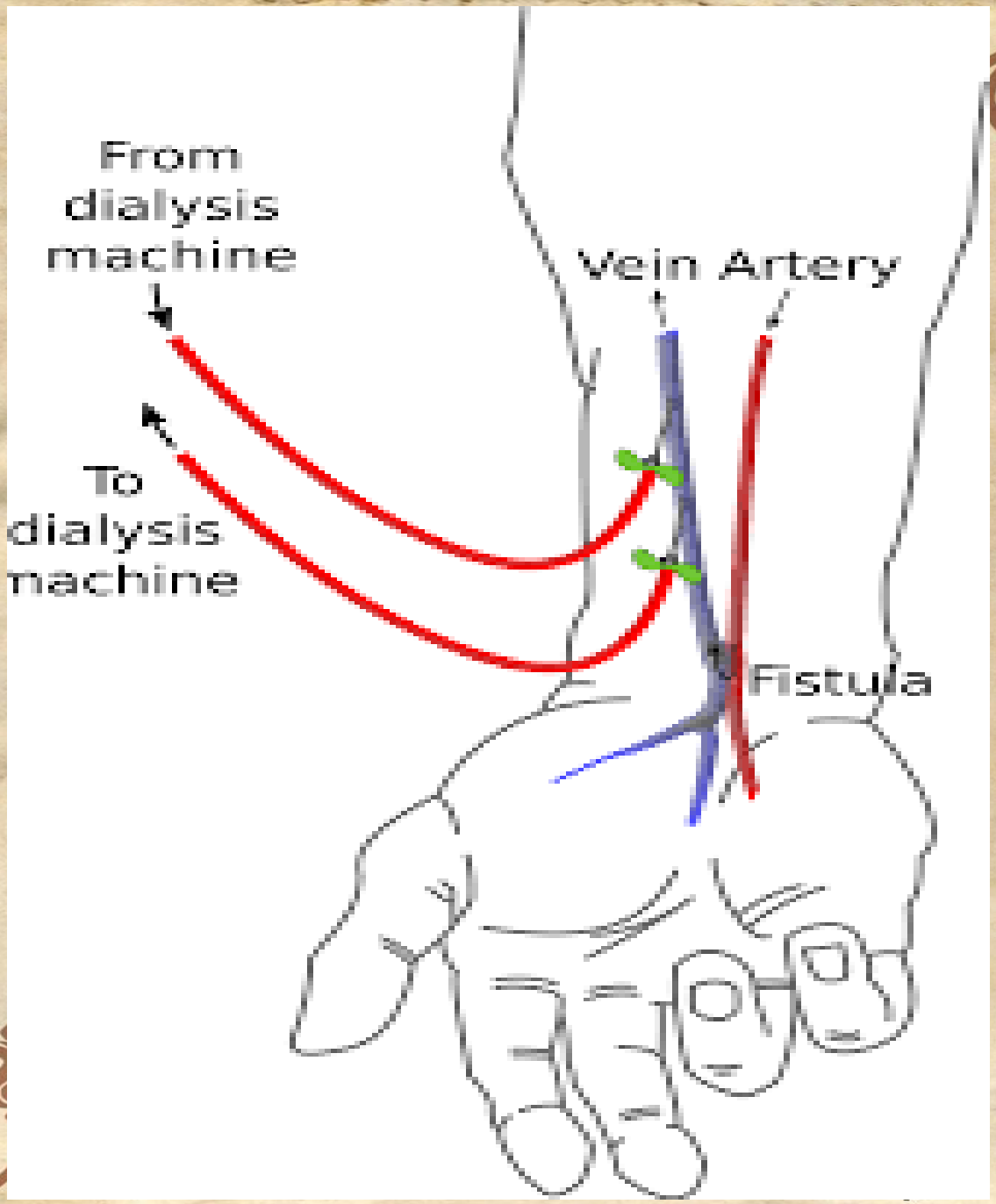
- ***Anemia prevalence begins with stage 3.***

- ***Shortened life cycle of red blood cells in uremia***

Cardiovascular disease

Patients with CKD tend to have many risk factors for CVD

- ✓ ***Every 1 mg per dL decrease in hemoglobin, a 6% increase in the risk of LVH***
- ✓ ***LVD – Fluid overload, shunting of blood through AV fistula for dialysis and anemia***
- ✓ ***Hypertension- Volume overload, ↑Peripheral vascular resistance, ↓Renal vasodilator prostaglandins, ↑RAAS activity***
- ✓ ***Dysregulation of calcium and phosphorous (An increase in serum phosphorous levels has been shown to stimulate vascular calcification)***
- ✓ ***Pericarditis – uremic state or dialysis***


From dialysis machine
To dialysis machine
Vein
Artery
Fistula

Disorders of calcium and phosphorus homeostasis

Hyperphosphatemia ⇒ ↓serum calcium by physiochemical interaction and complexation.

Serum calcium triggers the parathyroid gland to synthesize and secrete more parathyroid hormone (PTH).

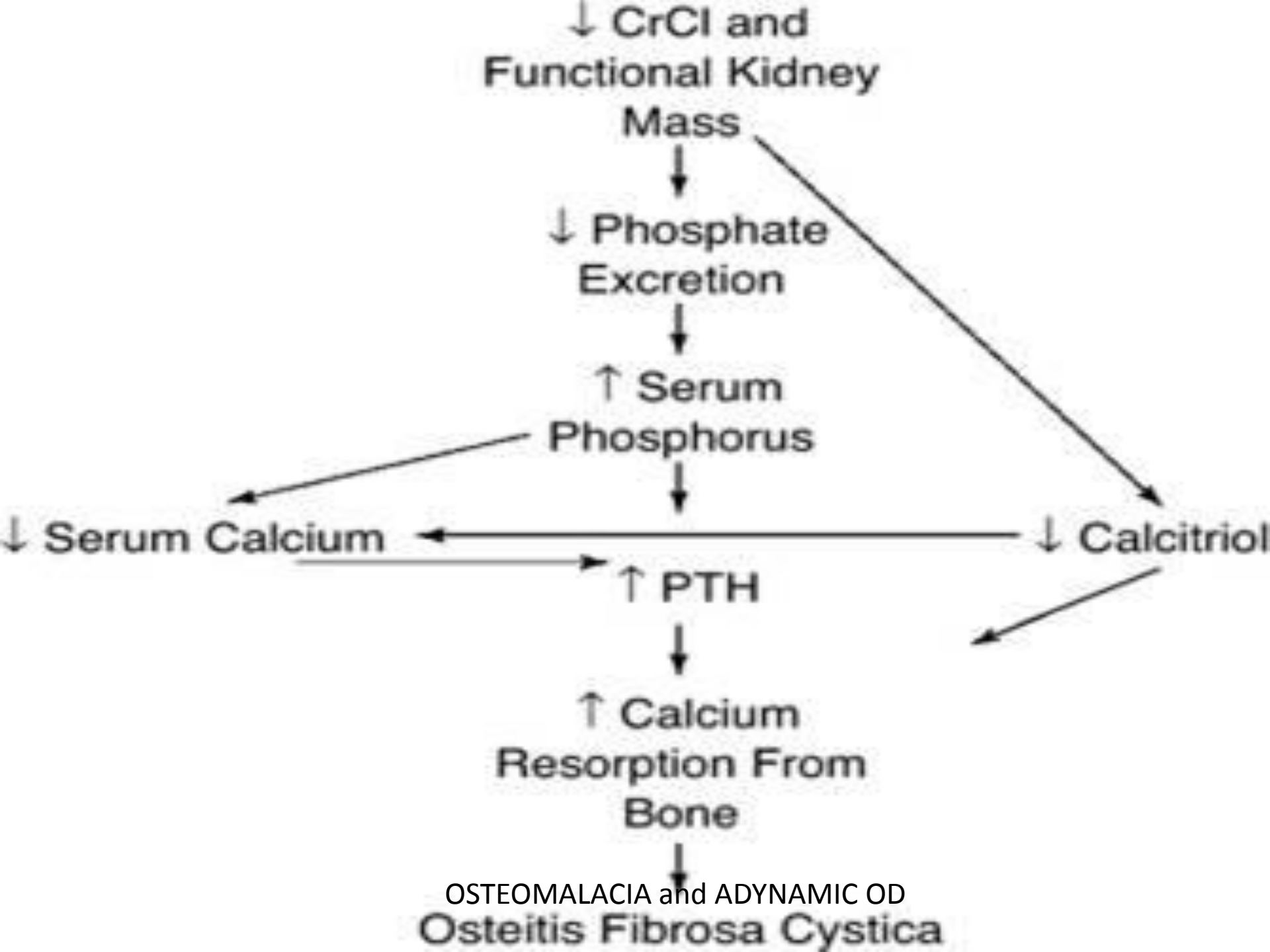
↑PTH in turn causes an increase in osteoclast activity in the bone, breaking down bone to release calcium and restore serum levels.

- *In kidney, the inactive vit D (25 OH vit D3) → active vit D (1,25 OH vit D3) or calcitriol in the presence of enzyme 1 α-hydroxylase.*

- *Active vitamin D (1,25-dihydroxyvitamin D or calcitriol)promotes increased intestinal absorption of calcium and has supression effect on PTH production.*

- ↓ *Calcitriol* - ↑ *PTH levels* → *Osteodystrophy (high bone or low bone turnover OD)*

- *Calcitriol also works directly on the parathyroid gland to suppress PTH production.*


↓ CrCl and
Functional Kidney
Mass
↓ Phosphate
Excretion
↑ Serum
Phosphorus
↓ Serum Calcium
↓ Calcitriol
↑ PTH
↑ Calcium
Resorption From
Bone
OSTEOMALACIA and ADYNAMIC OD
Osteitis Fibrosa Cystica

Sodium and Water

- ***Normal renal function guarantees that the tubular reabsorption of filtered sodium and water is adjusted so that urinary excretion matches net intake***

- ***Renal disease disrupt this glomerulotubular balance such that dietary intake of sodium exceeds its urinary excretion, leading to sodium retention and attendant extracellular fluid volume (ECFV) expansion***

Potassium Homeostasis

- ✓ ***90% to 95% of the daily potassium (dietary load)excreted by kidneys.***
- ✓ ***5% to 10% is excreted through the gut***
- ✓ ***In patients with CKD, distal tubular potassium secretion ↑ until the GFR is less than 20 mL/min per 1.73 m^2***
- ✓ ***End up with hyperkalemia***

Magnesium homeostasis

- ✓ ***The primary route of magnesium excretion is renal.***

- ✓ ***Mild, asymptomatic elevations in serum magnesium may occur in patients with advanced CKD***

Uremic Bleeding

uremia is the accumulation of substances in the blood, One such compound is guanidinosuccinic acid, a byproduct of ammonia detoxification.

Increase in nitric oxide,

Decrease platelet function

(By interfering with the interaction of fibrinogen and the platelet GP IIb/IIIa receptor)

Gastrointestinal Disorders

- ✓ ***Anorexia, nausea, and vomiting are common in patients with uremia, along with a metallic taste in the mouth that further depresses the appetite.***

- ✓ ***A possible cause of nausea and vomiting is the decomposition of urea by intestinal flora, resulting in a high concentration of ammonia.***

- ✓ ***PTH increases gastric acid secretion and contributes to gastrointestinal problems***

Disorders of Neural Function

- ✓ ***Neuropathy is caused by atrophy and demyelination of nerve fibers, possibly caused by uremic toxins.***
- ✓ ***Peripheral and central nervous system function affected***
- ✓ ***Restless legs syndrome (creeping, prickling, and itching sensations that are more intense at rest) is a manifestation of peripheral nerve involvement***
- ✓ ***uremic encephalopathy is a manifestation of central nervous system***
- ✓ ***These often are followed by an inability to fix attention, loss of recent memory, and perceptual errors in identifying persons and objects ,Delirium , coma & seizures***

Altered Immune Function

- ✓ ***All aspects of inflammation and immune function may be affected adversely by the high levels of urea and metabolic wastes***

Disorders of Skin Integrity

- ✓ ***Skin dryness** is caused by a reduction in size of sweat glands and the diminished activity of oil glands*

- ✓ ***Pruritus** is common from the high serum phosphate levels and the development of phosphate crystals.*

- ✓ ***In the advanced stages of untreated renal failure, urea crystals may precipitate on the skin***

- ✓ ***The fingernails may become thin and brittle, with a dark band just behind the leading edge of the nail, followed by a white band called Terry's nails.***

Sexual Dysfunction

- ✓ ***Cause is multifactorial high levels of uremic toxins, neuropathy, altered endocrine function, psychological factors, and medications***

- ✓ ***Impaired sexual function in women is manifested by abnormal levels of progesterone, luteinizing hormone, and prolactin.***

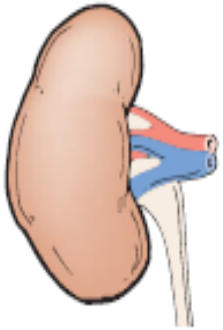
- ✓ ***Impaired sexual function in men is due to derangements of the pituitary and gonadal hormones, such as decreases in testosterone levels and increases in prolactin and luteinizing hormone levels, are common and cause erectile difficulties and decreased spermatocyte counts.***

METABOLIC ACIDOSIS

- ✓ ***The kidneys normally regulate blood pH by eliminating hydrogen ions produced in metabolic processes and regenerating bicarbonate.***

- ✓ ***This is achieved through hydrogen ion secretion, sodium and bicarbonate reabsorption, and the production of ammonia***

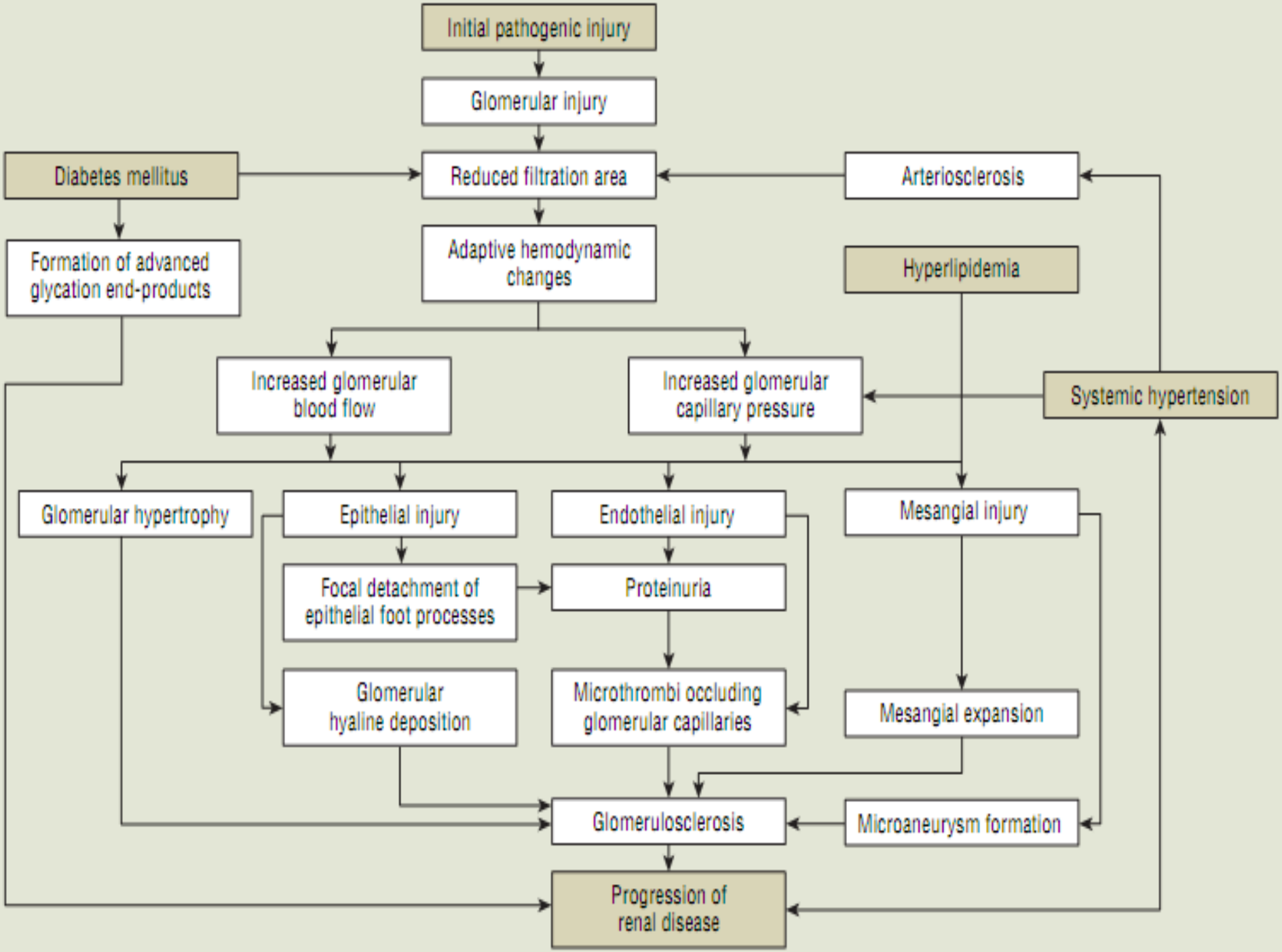
- ✓ ***With a decline in renal function, these mechanisms become impaired, and metabolic acidosis results.***



Chronic renal failure

- Sodium and water balance
  - Hypertension
  - Increased vascular volume
    - Edema
    - Heart failure
- Potassium balance
  - Hyperkalemia
- Elimination of nitrogenous wastes
  - Uremia
    - Coagulopathies
    - Pericarditis
    - Skin disorders
    - Gastrointestinal manifestations
    - Neurologic manifestations
    - Sexual dysfunction
- Erythropoietin production
  - Anemia
- Acid-base balance
  - Acidosis
  - Skeletal buffering
- Activation of vitamin D
  - Hypocalcemia
- Phosphate elimination
  - Hyperparathyroidism

Osteodystrophies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