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Nutritional Medicine in Kidney Disease

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The Kidneys

- Human Kidneys weigh less than 1% of total body weight
- But receives 20% of cardiac output
- The kidneys premiere role in filtering toxins from blood and the resorption of glomerular filtrate exposes kidney tubular cells (epithelial cells that line the nephrons, also known as renal cells) to many environmental toxins, drugs, intermediates of drug metabolism and end-products of metabolism, including those related to supplements intake.
- In recent years we have seen escalating incidence of chronic kidney disease due to these effects, as well as the impact of increased incidence of obesity and type II diabetes.

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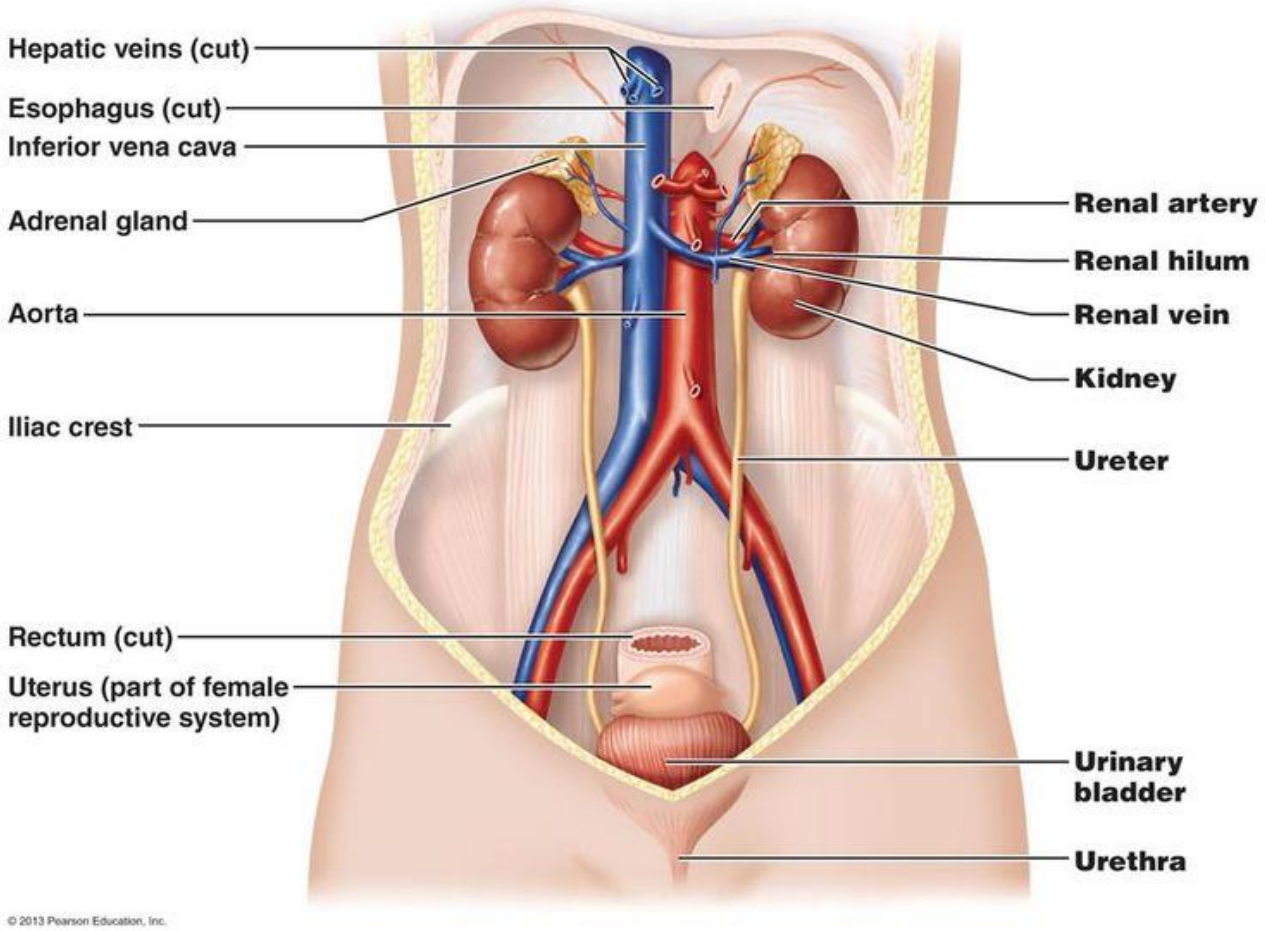
Anatomy



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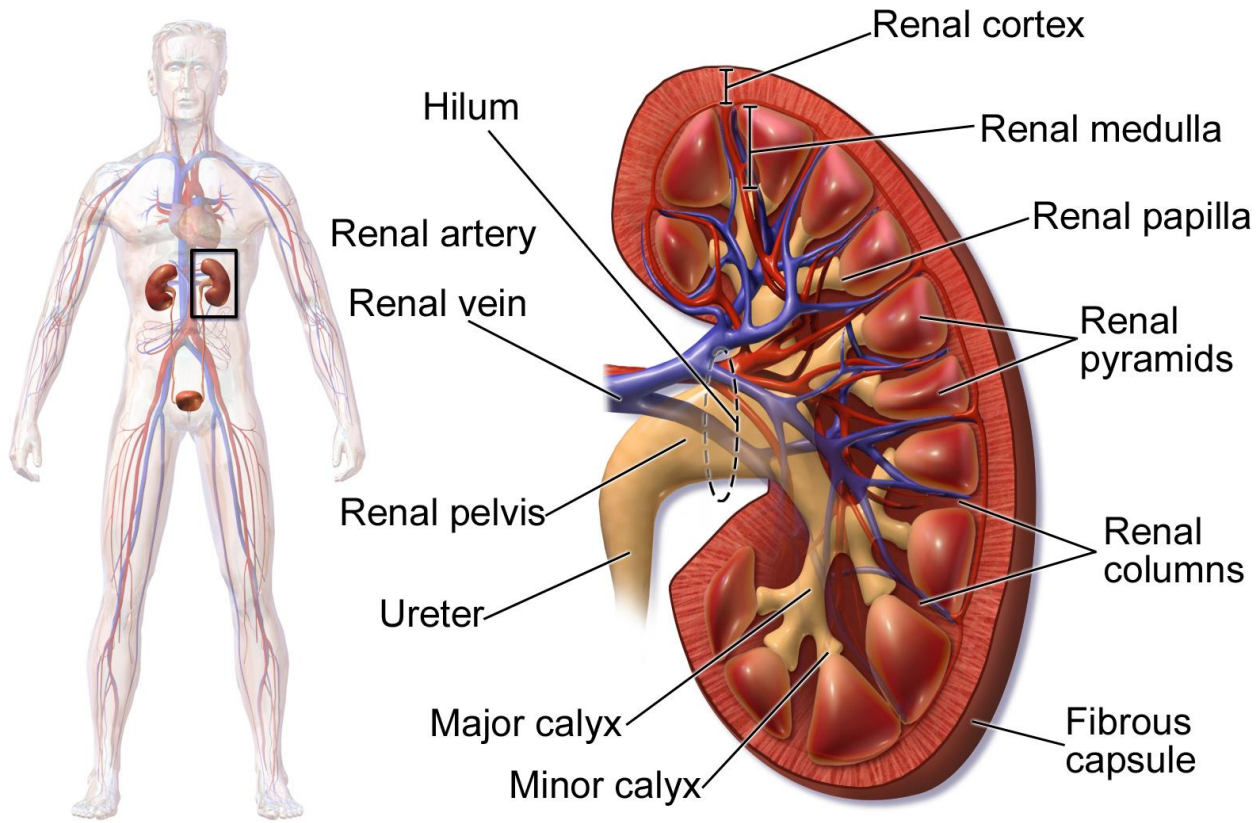

Kidney Anatomy

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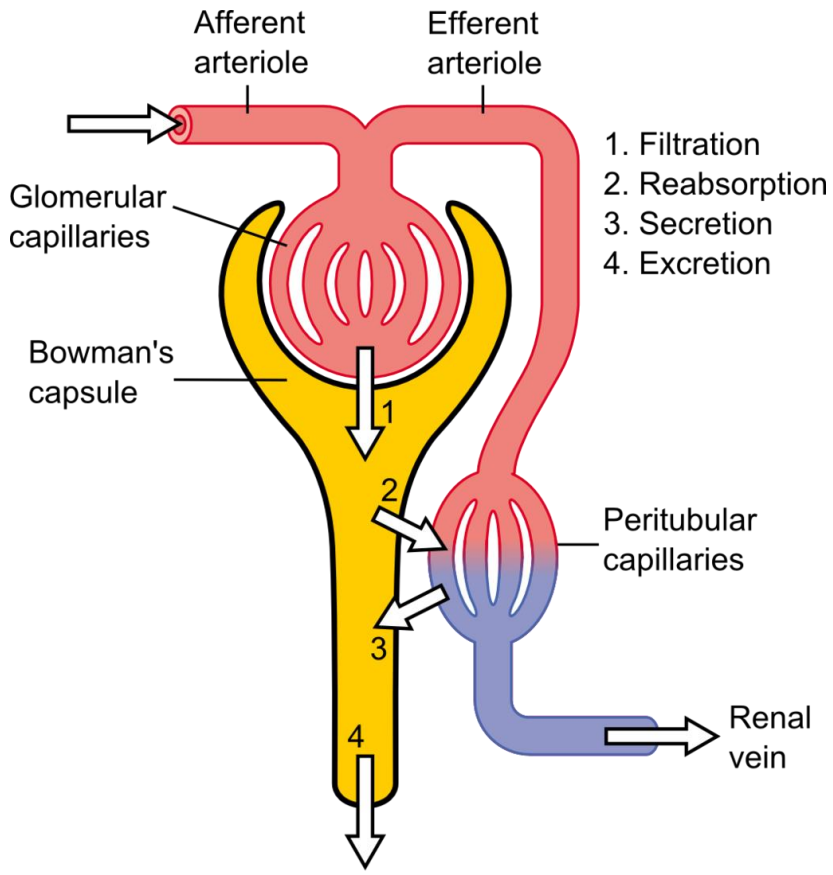
Basic Scheme of Blood Flow and Filtration



Excretion = Filtration – Reabsorption + Secretion

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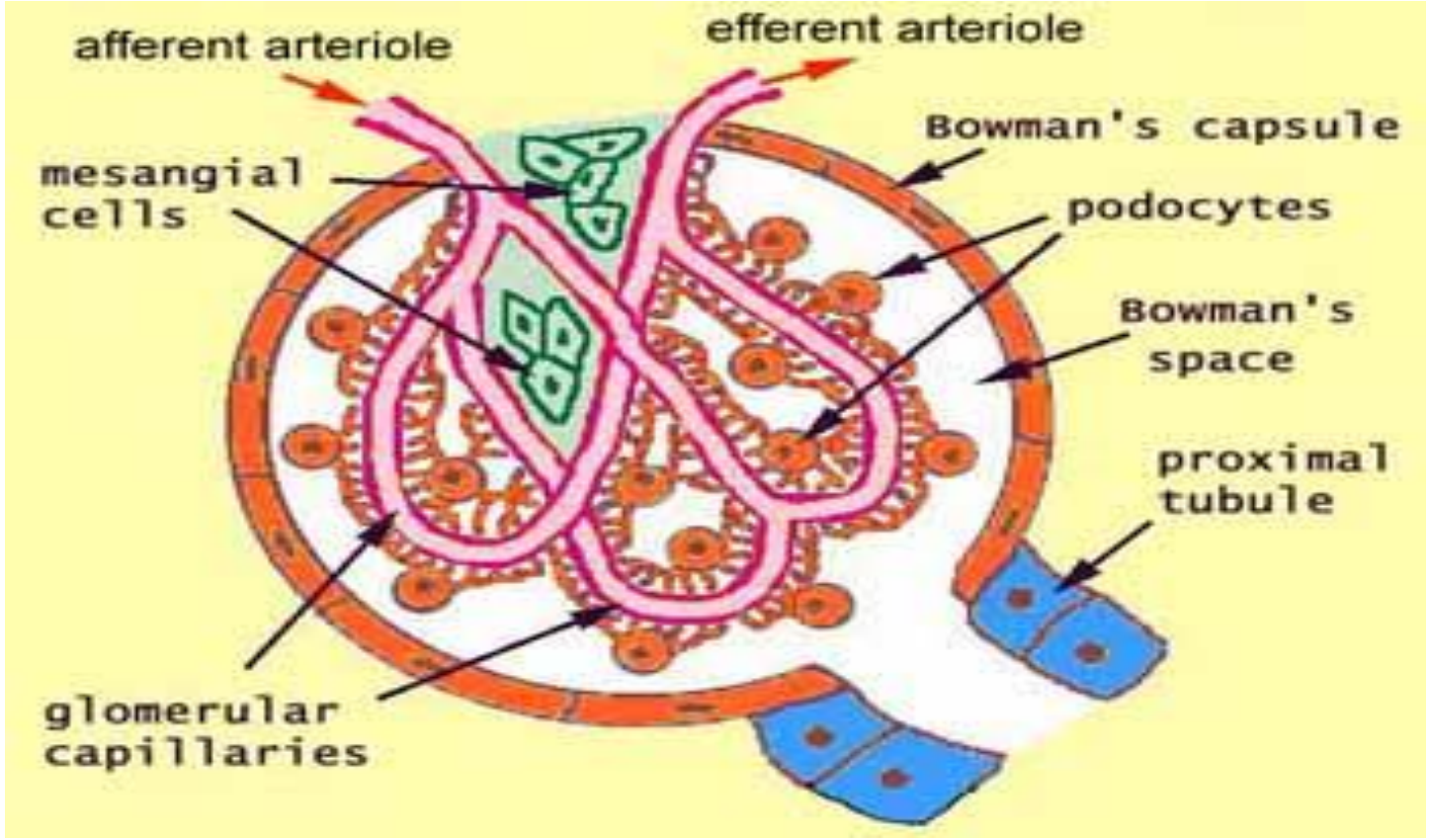
Glomerulus and Bowman's Capsule



Ultrafiltration

Blood flows into glomerulus form afferent arteriole.

This is wider the efferent arteriole. This difference ensures pressure is higher in glomerulus than the Bowman's capsule, pushing fluid from the blood into Bowman's capsule. Basement membrane stops bloods cells and proteins passing through. Podocytes allow fluid to travel between them into Bowman's capsule.

Filtered Out of Blood

Water
Amino Acids
Glucose
Urea
Inorganic Ions (salts)

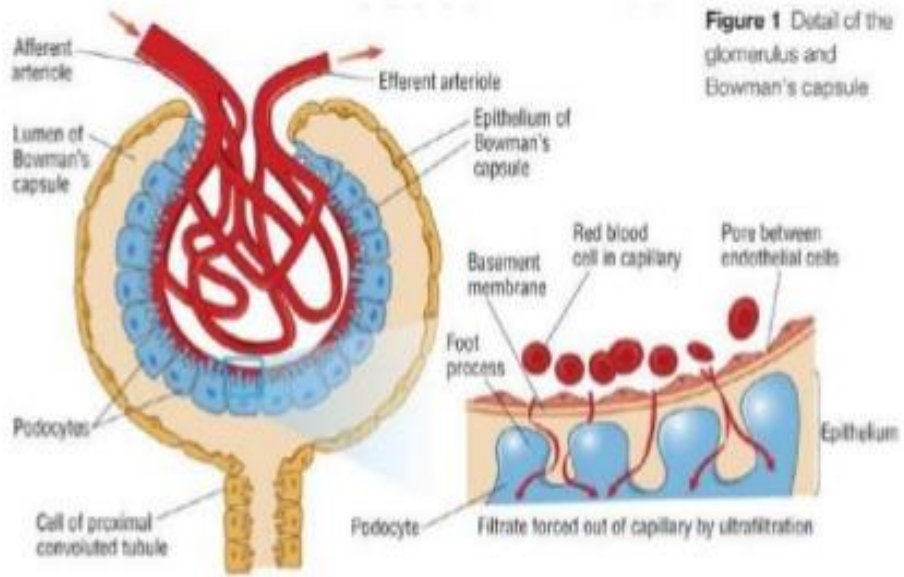


Figure 1 Detail of the glomerulus and Bowman's capsule

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Glomerulus and Bowman's Capsule

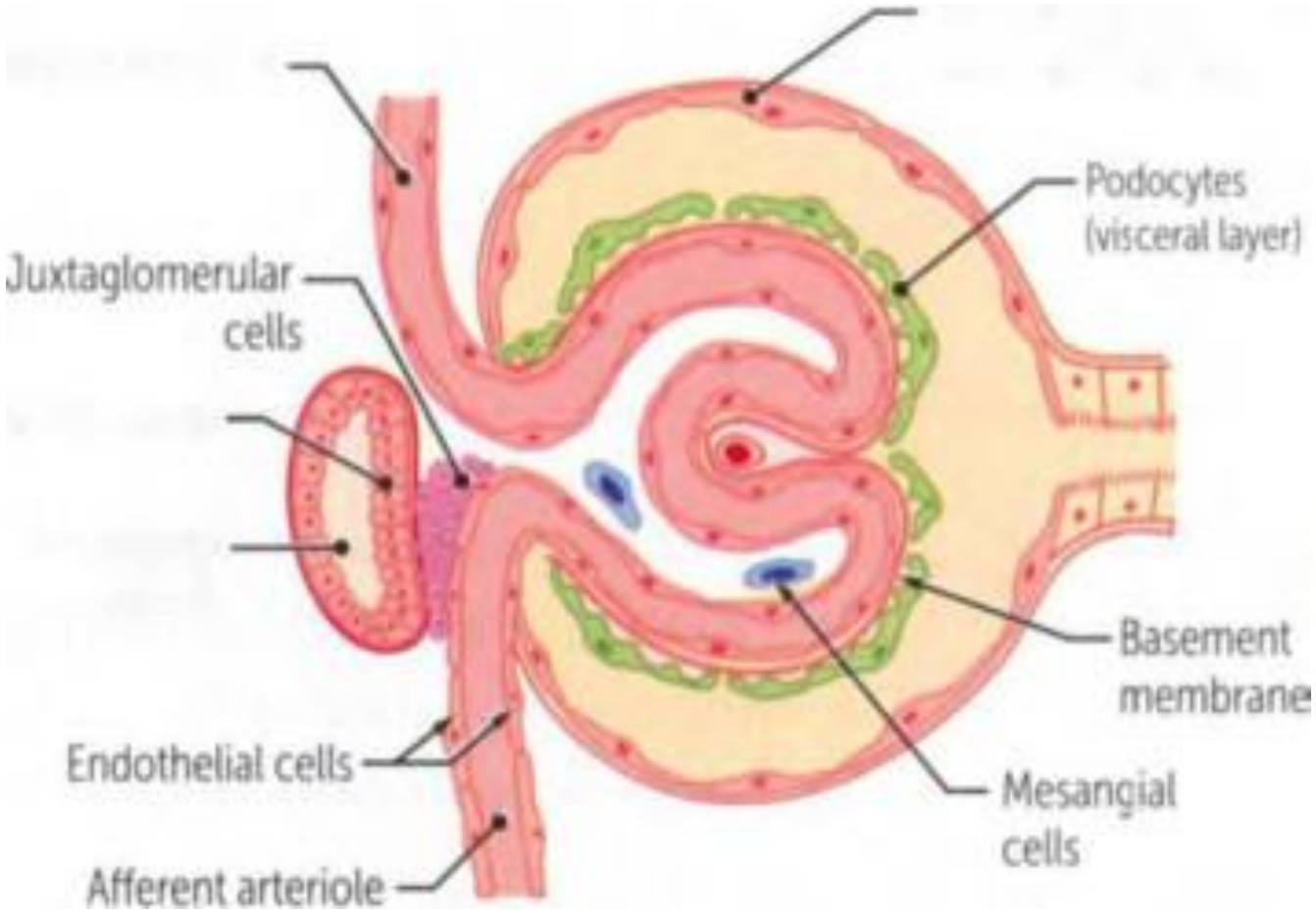

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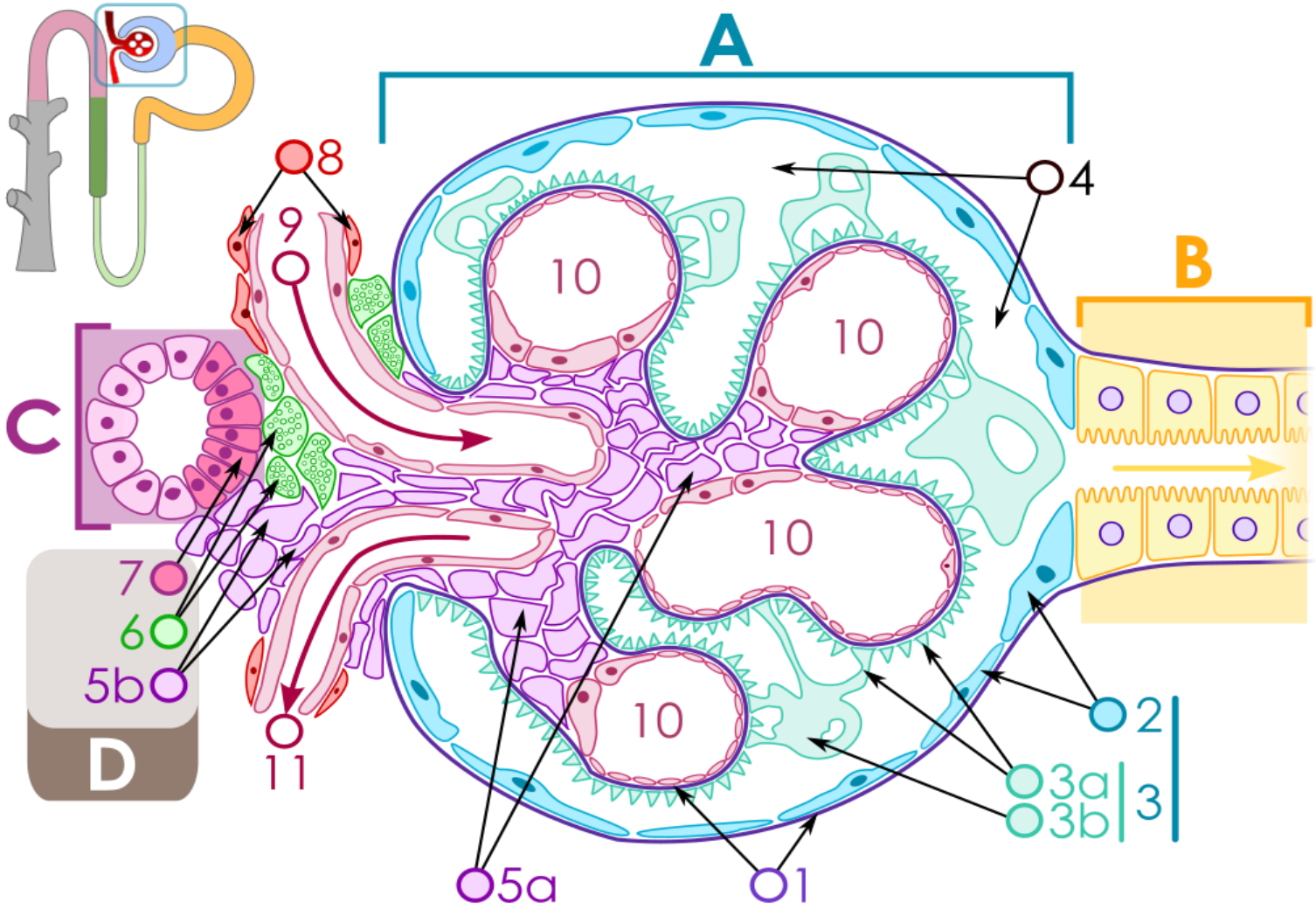
Diagram of renal corpuscle structure: A – Renal corpuscle B – Proximal tubule C – Distal convoluted tubule D – Juxtaglomerular apparatus 1. Basement membrane (Basal lamina) 2. Bowman's capsule – parietal layer 3. Bowman's capsule – visceral layer 3a. Pedicels (Foot processes from podocytes) 3b. Podocyte 4. Bowman's space (urinary space) 5a. Mesangium – Intraglomerular cell 5b. Mesangium – Extraglomerular cell 6. Granular cells (Juxtaglomerular cells) 7. Macula densa 8. Myocytes (smooth muscle) 9. Afferent arteriole 10. Glomerulus Capillaries 11. Efferent arteriole



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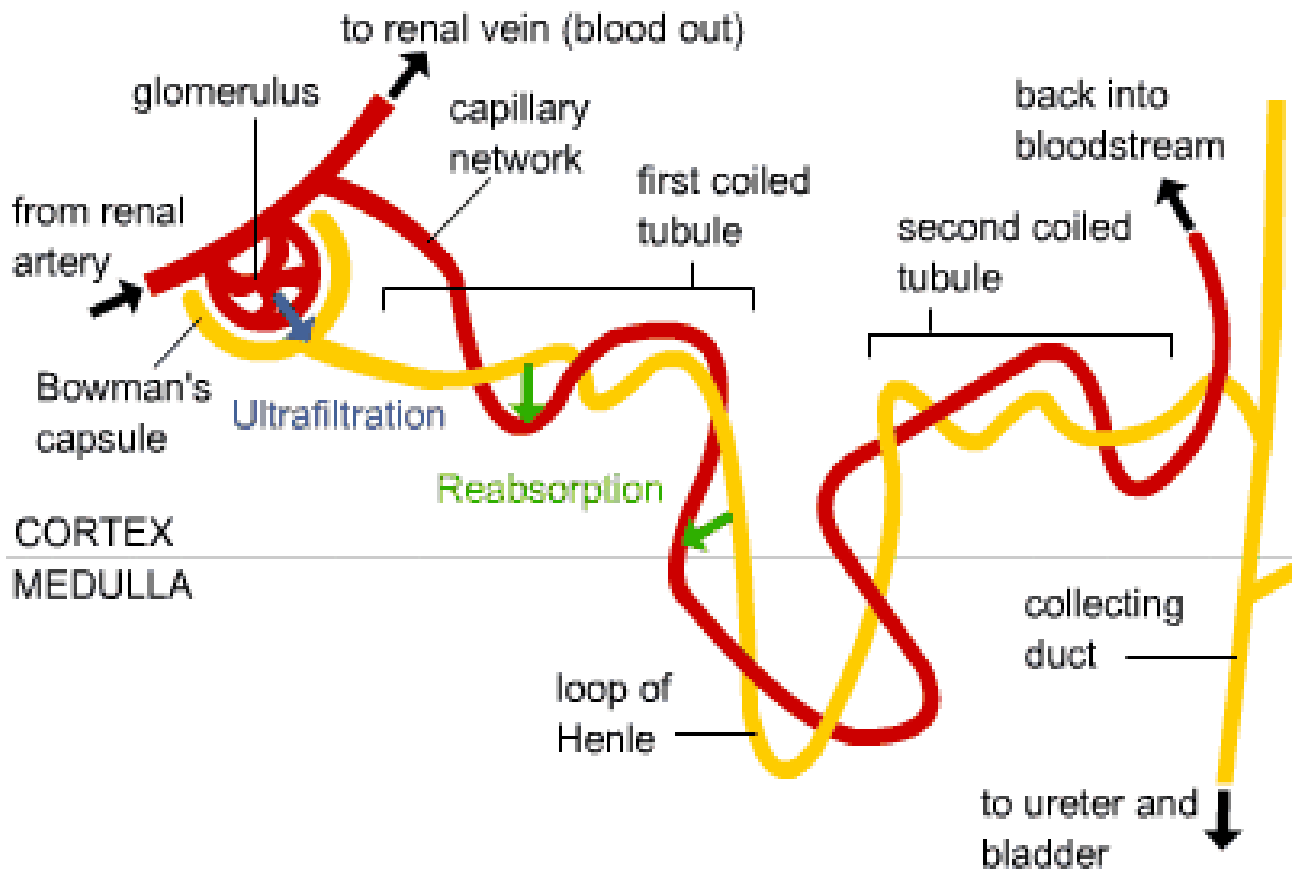
Capillary Network and Nephron



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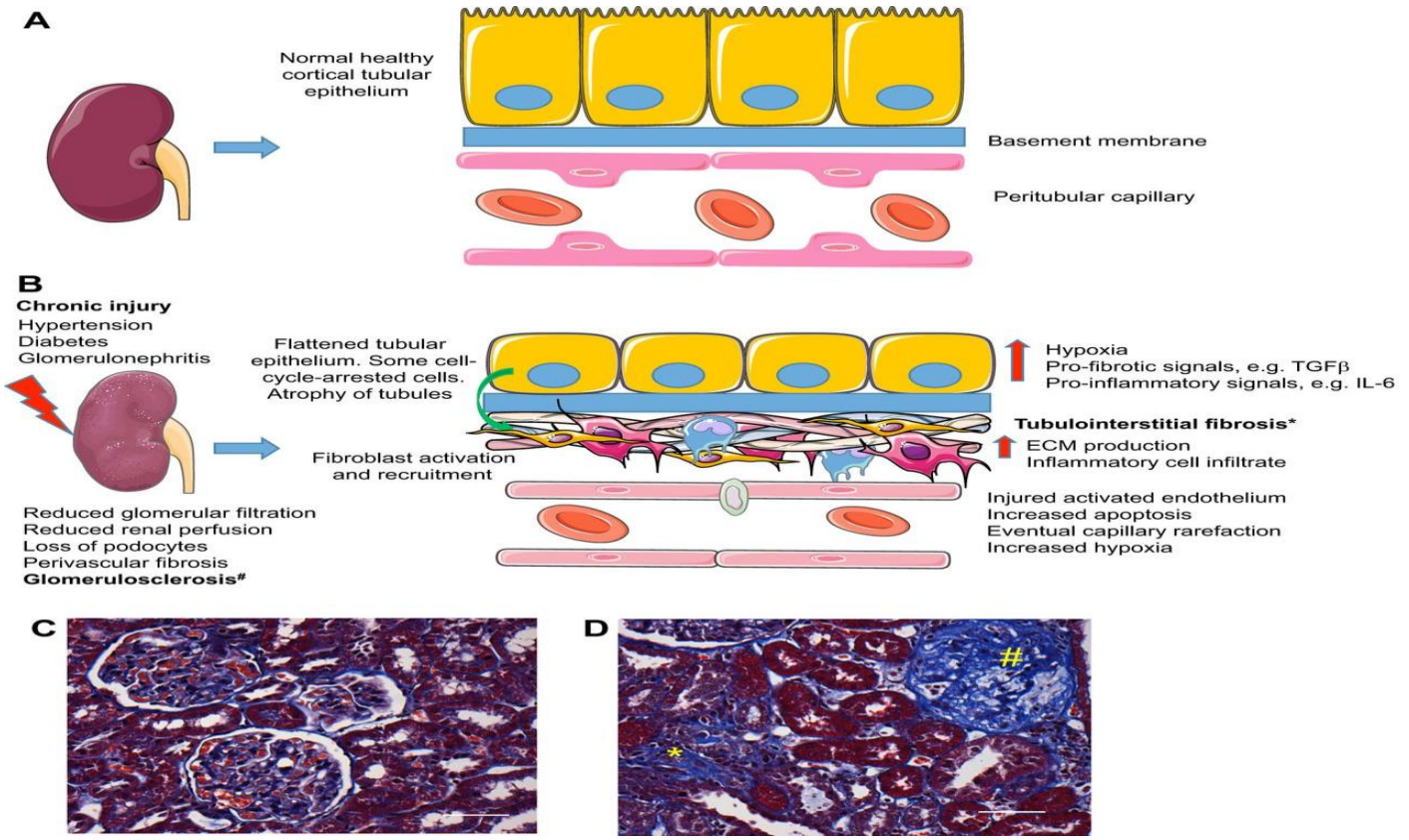
Renal Tubular Cells = epithelial cells that line nephrons



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Kidney Function

- The nephron is the microscopic structural and functional unit of the kidney. It is composed of a renal corpuscle and a renal tubule.
- A healthy adult has 0.8 to 1.5 million nephrons in each kidney.
- The renal corpuscle consists of a tuft of capillaries called a glomerulus and an encompassing Bowman's capsule.
- The renal tubule extends from the capsule. The capsule and tubule are connected and are composed of epithelial cells with a lumen.
- Blood is filtered as it passes through three layers: the endothelial cells of the capillary wall, its basement membrane, and between the foot processes of the podocytes of the lining of the capsule.

- The tubule has adjacent peritubular capillaries that run between the descending and ascending portions of the tubule.

- As the fluid from the capsule flows down into the tubule, it is processed by the epithelial cells lining the tubule: water is reabsorbed and substances are exchanged (some are added, others are removed); first with the interstitial fluid outside the tubules, and then into the plasma in the adjacent peritubular capillaries through the endothelial cells lining that capillary.

- This process regulates the volume of body fluid as well as levels of many body substances. At the end of the tubule, the remaining fluid—urine—exits: it is composed of water, metabolic waste, and toxins.

- Normally the only components of the blood that are not filtered into Bowman's capsule are blood proteins, red blood cells, white blood cells and platelets.

- Over 150 liters of fluid enter the glomeruli of an adult every day: 99% of the water in that filtrate is reabsorbed. Reabsorption occurs in the renal tubules and is either passive, due to diffusion, or active, due to pumping against a concentration gradient.

- Secretion also occurs in the tubules and is active. Substances reabsorbed include: water, sodium, chloride, glucose, amino acids, lactate, magnesium, calcium, phosphate, ur ic acid, and bicarbonate.

- Substances secreted include urea, creatinine, potassium, hydrogen, and uric acid.

- Some of the hormones which signal the tubules to alter the reabsorption or secretion rate, and thereby maintain homeostasis, include (along with the substance affected) antidiuretic hormone (water), aldosterone (sodium, potassium), parathyroid hormone (calcium, phosphate), atrial natriuretic peptide (sodium) and brain natriuretic peptide (sodium).

- A countercurrent system in the renal medulla provides the mechanism for generating a hypertonic interstitium, which allows the recovery of solute-free water from within the nephron and returning it to the venous vasculature when appropriate.

- Some diseases of the nephron predominantly affect either the glomeruli or the tubules.

- Glomerular diseases include diabetic nephropathy, glomerulonephritis and IgA nephropathy.

- Renal tubular diseases include acute tubular necrosis and polycystic kidney disease.

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The Nephron

- The nephron is the structural and functional unit of the kidney. Each adult kidney contains around one million nephrons.

- Nephron utilizes four processes to alter the blood plasma which flows to it: filtration, reabsorption, secretion, and excretion.

- Via one or more of these mechanisms, the kidney participates in the control of the volume of various body fluid compartments, fluid osmolality, acid-base balance,
various electrolyte concentrations, and removal of toxins

- Filtration occurs in the glomerulus: one-fifth of the blood volume that enters the kidneys is filtered. Examples of substances reabsorbed are solute-free water, sodium, bicarbonate, glucose, and amino acids.

- Examples of substances secreted
  are hydrogen, ammonium, potassium and uric acid

- The kidneys also carry out functions independent of the nephron. For example, they convert a precursor of vitamin D to its active form – calcitriol – and synthesize
  the hormones erythropoietin and renin.

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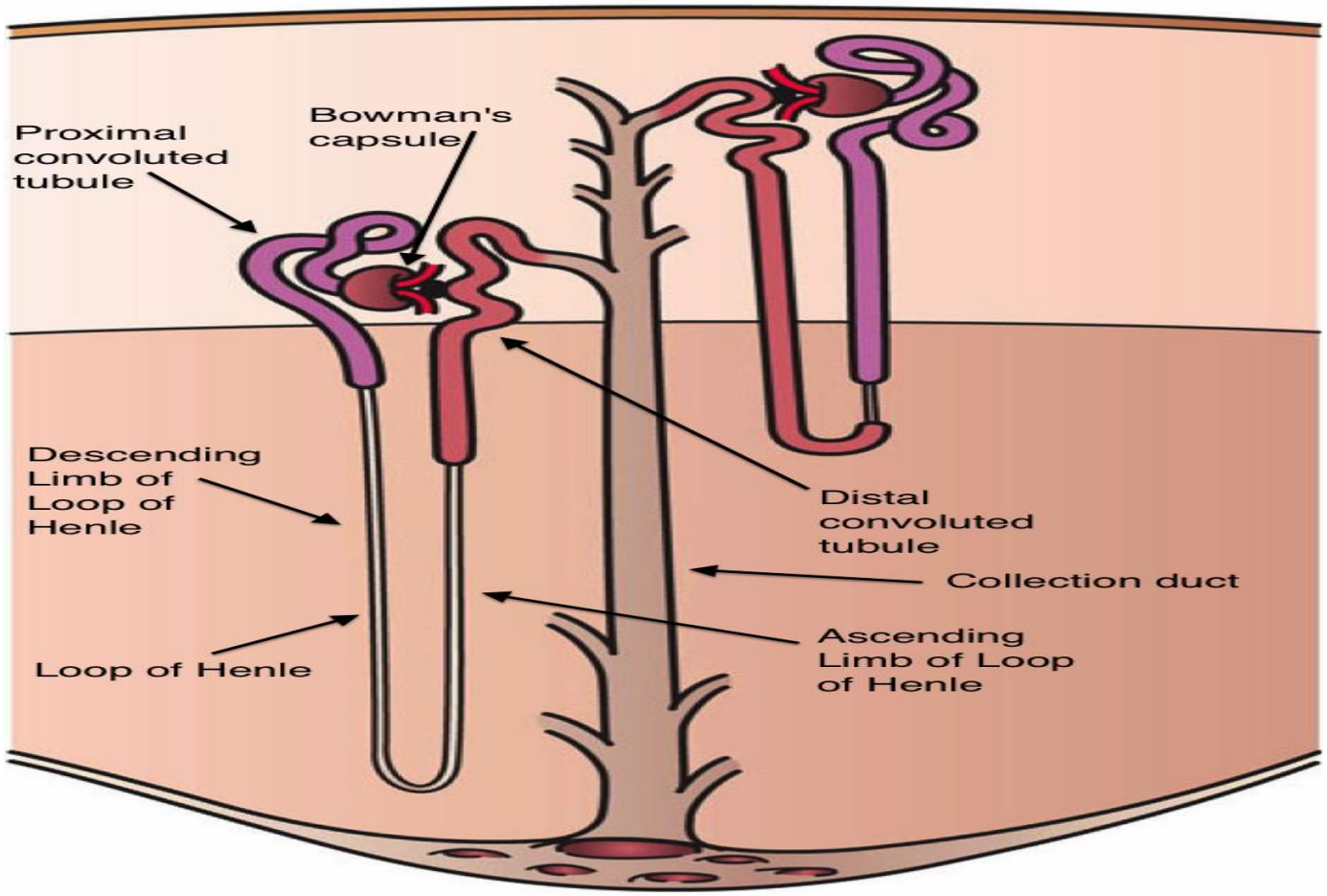
Nephrons



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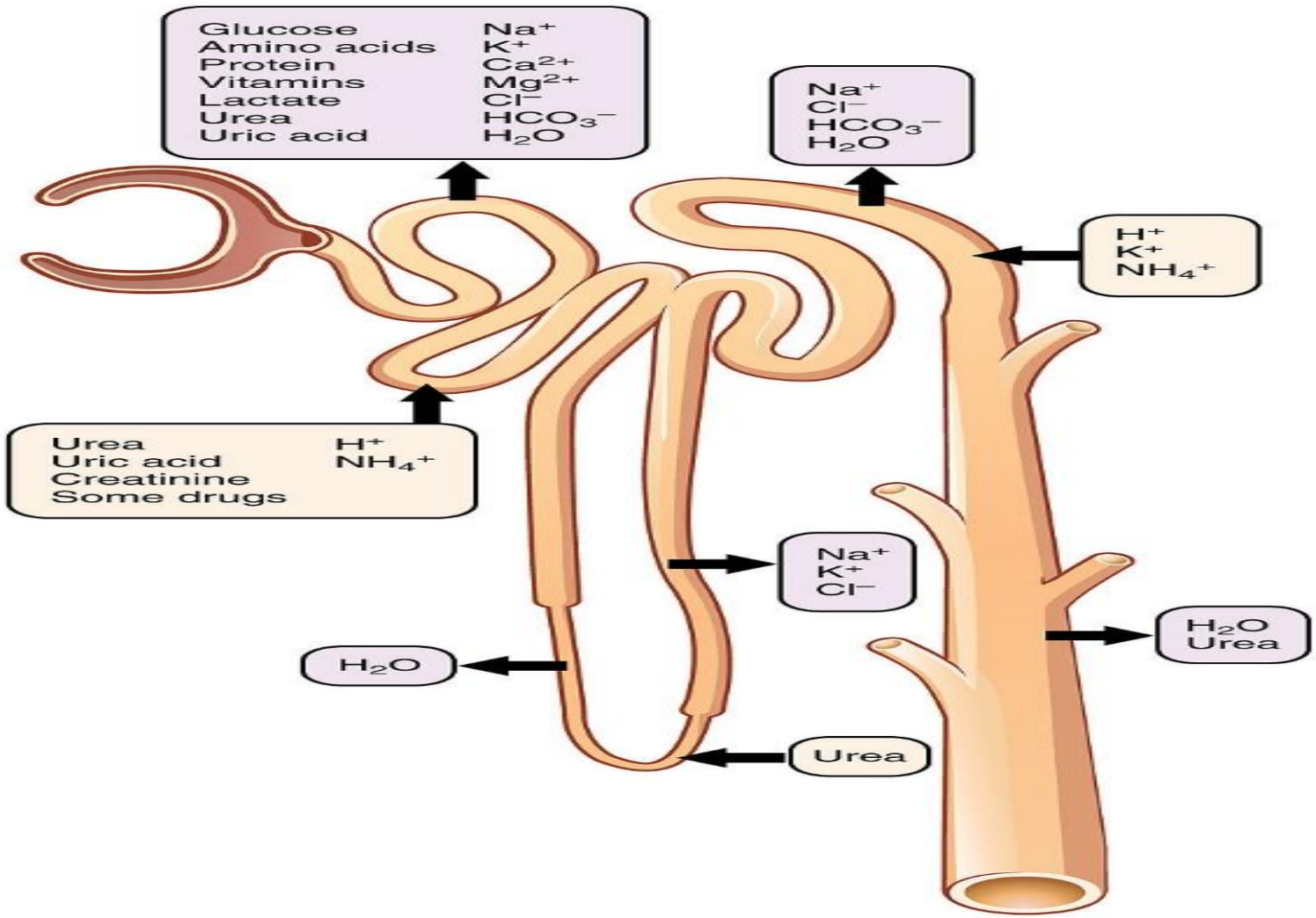
Resorption and Excretion



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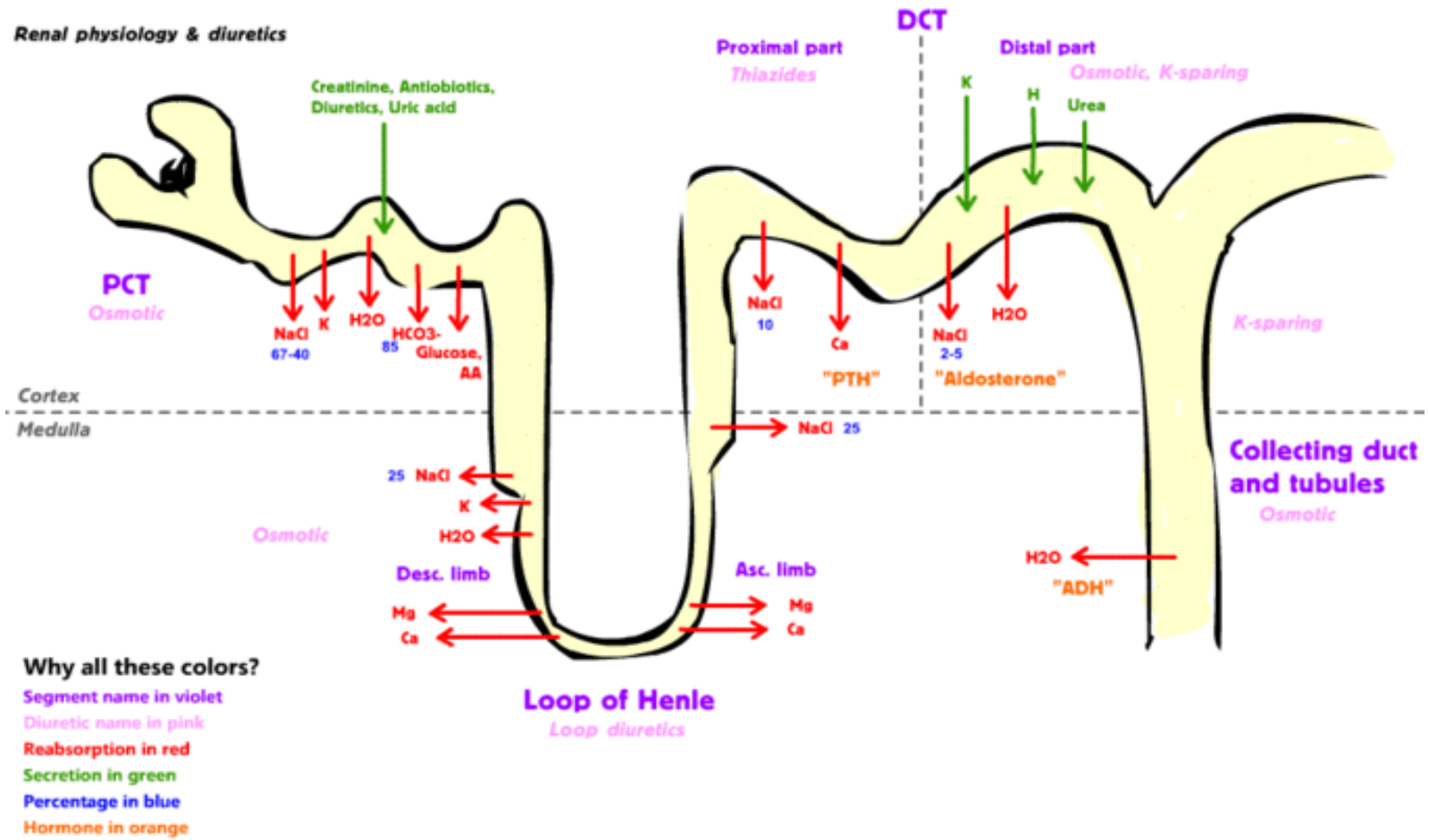
Resorption and Secretion



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Podocytes

- Podocytes are cells in the Bowman's capsule in the kidneys that wrap around capillaries of the glomerulus· The Bowman's capsule filters the blood, retaining large molecules such as proteins while smaller molecules such as water, salts, and sugars are filtered as the first step in the formation of urine.

- Although various viscera have epithelial layers, the name visceral epithelial cells usually refers specifically to podocytes, which are specialized epithelial cells that reside in the visceral layer of the capsule.

- The podocytes have long processes, called foot processes, foot projections, or pedicels. The foot projections wrap around the capillaries and leave slits between them.

- Blood is filtered through these slits, each known as a filtration slit or slit diaphragm.

- Podocytes are also involved in regulation of glomerular filtration rate (GFR). When podocytes contract, they cause closure of filtration slits. This decreases the GFR by reducing the surface area available for filtration.

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Juxtaglomerlar Apparatus:

- The juxtaglomerular apparatus is a specialized region associated with the nephron, but separate from it.

- It produces and secretes into the circulation the enzyme renin (angiotensinogenase), which cleaves angiotensinogen and creates angiotensin-1 which is then converted by angiotensin converting enzyme (ACE) to angiotensin-2, a potent vasoconstrictor: the renin–angiotensin system.

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Kidney Hormones

- The kidneys secrete a variety of hormones, including erythropoietin, and the enzyme renin.
- Erythropoietin is released in response to hypoxia (low levels of oxygen at tissue level) in the renal circulation.
- It stimulates erythropoiesis (production of red blood cells) in the bone marrow.
- Calcitriol, the activated form of vitamin D, promotes intestinal absorption of calcium and the renal reabsorption of phosphate.
- Part of the renin–angiotensin–aldosterone system, renin is an enzyme involved in the regulation of aldosterone levels.

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Kidney Assessment

- Procedures used in the management of kidney disease include chemical and microscopic examination of the urine (urinalysis), measurement of kidney function by calculating the estimated glomerular filtration rate (eGFR) using the serum creatinine; and kidney biopsy and CT scan to evaluate for abnormal anatomy.

- Dialysis and kidney transplantation are used to treat kidney failure; one (or both sequentially) of these are almost always used when renal function drops below 15%. Nephrectomy is frequently used to cure renal cell carcinoma.

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Kidneys' Role in Detoxification

- The liver is the primary site of phase I and phase II detoxification, but most epithelial cells also have these detox pathways for their own purposes.

- The kidneys are the second most important organ cells that possess these pathways and thus kidney cells are exposed to high levels of xenobiotic and other metabolites that can damage their structure and function (drugs, supplements, pesticides, etc.).

- The epithelial cells of the kidney are termed tubular cells or renal cells.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3791982/

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Renal Tubular Cell Damage and Repair

- Kidney tubules are an essential component of an organism's blood clearance mechanism, recovering essential metabolites from glomerular filtration by active transport.

- Tubules are subject to injury, usually as the result of ischemia–reperfusion events that damage the polarized tubular cell layer that coats the tubule basement membrane, causing dysfunction and necrosis that is often associated with acute renal failure.

- However, tubules are capable of self-repair, forming new proximal tubular cells to replace failing or necrotic cells. The origin of the progenitor cells that give rise to new tubular cells is unknown.

- At one extreme, it is possible that all or a fraction of tubular cells can undergo a form of dedifferentiation and subsequent mitosis to form new tubular cells, or alternatively, it is possible that tubular regeneration follows the stem cell/transit-amplifying cell paradigm described for more rapidly regenerating organ systems.

- Regardless of the mechanism employed to generate new tubular cells, human tubular cells are readily grown in primary cultures and can recapitulate many of the metabolic, endocrine, and immunological properties attributable to endogenous renal proximal tubules when engrafted into bioartificial devices.

- Thus, impressive regenerative abilities after drug, supplement, toxin or disease insult if offender is removed in time. With heavy supplementation program kidney function should be monitored.

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- **Renal Tubular Secretion:** Drugs that are not filtered in the kidney leave the glomerulus by the efferent renal arterioles, which branch to form the peritubular capillary system. Drugs in the blood may pass through the fenestrated capillary endothelium and diffuse down a concentration gradient into the interstitial fluid.

- Here, drugs may bind to high-affinity organic-acid or organic-base secretory proteins, which are located on the basolateral and apical membranes of the proximal tubule cells.

- These organic-acid and organic-base proteins provide a relatively nonspecific active transport pathway for anionic and cationic drugs, respectively, to gain access into cells of the proximal tubule and to be secreted into the tubular lumen and urine (i.e., renal tubular secretion)

- https://www.sciencedirect.com/topics/neuroscience/nephron

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Importance Of Osmoprotectants

- **Osmoprotectants** are small organic molecules with neutral charge and low toxicity at high concentrations that act as osmolytes and help organisms survive extreme osmotic stress.

- Osmoprotectants can be placed in three chemical classes: betaines and associated molecules, sugars and polyols, and amino acids. These molecules accumulate in cells and balance the osmotic difference between the cell's surroundings and the cytosol.

- Osmolytes - They are soluble in the solution within a cell, or in the surrounding fluid, e.g. as plasma osmolytes. They play a role in maintaining cell volume and fluid balance. For example, when a cell swells due to external osmotic pressure, membrane channels open and allow efflux of osmolytes which carry water with them, restoring normal cell volume.

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Betaine

- It is now well-established that the primary role of betaine in the kidney is osmoprotection. The always high but changing extracellular osmolarity in the kidney medulla plays an essential role in urine concentration.

- To balance the high osmolarity and preserve cell volume without interfering with cell function, one well-characterized mechanism is to accumulate compatible osmolyte (Miyakawa et al., 1999a.

- Betaine, sorbitol, myo-inositol, taurine, and glycerolphosphorylcholine are the predominant osmolytes in the mammalian kidney cells (Bagnasco et al., 1986).

- The accumulation of betaine is primarily due to the presence of BGT1 (Betaine;GABA Trasnporter-1) and is influenced by tonicity (Nakanishi et al., 1990; Yamauchi et al., 1992; Handler and Kwon, 1996).

- Because the novel transporter was able to transport not only GABA, but also betaine, it was named the betaine-GABA transporter (BGT1; slc6a12).

Reference

- https://www.frontiersin.org/articles/10.3389/fphys.2014.00159/full

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- The always high (but changing) osmolarity in the interstitium of the inner medulla is essential for the normal process of water reabsorption and urine concentration.

- The high osmolarity contributes to a ‘hostile environment' and an essential strategy for cellular survival is to accumulate osmotically active organic compounds.

- These balance the high extracellular osmolarity and preserve cell volume without interfering with cell function. This aids survival because cell shrinkage would facilitate apoptosis.

- Betaine is an important osmolyte in the kidney and in other tissues such as brain. Betaine is present in blood plasma at about 0.1 mM and is derived from the diet and choline metabolism in the liver.

- In contrast to reabsorption of filtered betaine by the proximal tubule in the cortex, cells in the kidney medulla accumulate betaine **primarily from the blood supply and via the sodium and chloride coupled betaine/γ-aminobutyric acid GABA transport system (BGT1). Thus, higher intakes choline, which can be oxidized to betaine, or betaine supplementation may improve osmoprotectant function of tubular cells in patients on polypharmacy, heavy supplement dosages, or other states that increases interstitial hyperosmolarity. Drinking more water may also help to reduce osmolarity impact of drugs and heavy supplement use.**

https://www.karger.com/Article/FullText/356622

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Taurine

- There are a number of amino acids and amino acid derivatives that act as osmoprotectants, including glycine, proline, isoleucine, leucine, phenylalanine, valine, β-alanine, taurine, and hypotaurine.

- Taurine, a sulfur-containing β-amino acid, represents the predominant amino acid osmolyte serving as an osmoprotectant in mammals. It is derived from cysteine and formed principally by the liver and then released into the systemic circulation. At least within the kidney, increased taurine transport (rather than synthesis) appears to drive intracellular accumulation during hypertonicity.

- The solute carrier family 6, member 6 (SLC6A6), previously known as taurine transporter (TauT) protein, is responsible for taurine transport across the plasma membrane and, like many other genes, is regulated by NFAT5 during hyperosmotic stress.

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- As the synthesis of both taurine and glutathione (GSH) requires cysteine, it is feasible that, during increased osmotic stress where oxidative stress is significantly elevated, these metabolic pathways may compete for the intracellular cysteine pool.

- Studies have revealed that taurine also influences a number of processes unrelated to its role in osmotic stress. Taurine has been implicated in regulating cardiac rhythm, cardiac contractile function, and blood pressure

Reference -
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3438915/

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Drugs Damaging Kidneys -Recommendations From the National Kidney Foundation

- Heavy or long-term use of some of these medicines, such as ibuprofen, naproxen, and higher dose aspirin, can cause chronic kidney disease known as chronic interstitial nephritis.

- The warning labels on over-the-counter analgesics tell you not to use these medicines for more than l0 days for pain and more than three days for fever.

- If you have pain and/or fever for a longer time, you should see your doctor. The doctor can check for possible medical problems and advise you about what medications you should take.

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Is Aspirin safe for regular use?

- When taken as directed, regular use of aspirin does not seem to increase the risk of kidney disease in people who have normal kidney function.

- However, taking doses that are too large (usually more than six or eight tablets a day) may temporarily- and possibly permanently- reduce kidney function.

- In people with kidney disease, aspirin may increase the tendency to bleed. People who already have reduced kidney function, or other health problems such as liver disease or severe heart failure, should not use aspirin without speaking to their doctor.

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My doctor recommended that I take an aspirin every day to prevent heart attacks. Will this hurt my kidneys?

- No. There is no evidence of risk regarding the regular use of aspirin in the small doses recommended for prevention of heart attacks.

- Use of a ‘baby aspirin’ (81-162 mg daily) is fine, even with reduced kidney function.

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What analgesics are safe for people who have kidney disease?

- Acetaminophen remains the drug of choice for occasional use in patients with kidney disease because of bleeding complications that may occur when these patients use aspirin.

- However, kidney patients who need to use acetaminophen habitually should be supervised by their doctors and be sure to avoid drinking alcohol while on this medicine.

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NSAIDs? Are they safe to take?

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are a specific group of pain relievers. Some NSAIDs are available over the counter. This includes different brands of ibuprofen, naproxen sodium and ketoprofen.

- NSAIDs are usually safe for occasional use when taken as directed, but if you have known decreased kidney function, they should be avoided.

- These medications should only be used under a doctor's care by patients with kidney disease, heart disease, high blood pressure or liver disease or by people who are over 65 or who take diuretic medications.

- NSAIDs may cause an increased risk of sudden kidney failure and even progressive kidney damage.

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Are there other side effects from taking aspirin and NSAIDs?

- Yes. The development of stomach ulcers and gastrointestinal bleeding has been the most common serious side effect from taking NSAIDs and aspirin.

- NSAIDs also increase the risk of heart attack and stroke.

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What can I do to keep my kidneys healthy?

Kidney disease caused by analgesics is often preventable Here are some things you can do to help keep your kidneys healthy.

- Do not use over-the-counter pain relievers more than 10 days for pain or more than three days for fever. If you have pain or fever for a longer time, you should see your doctor.

- Avoid prolonged use of analgesics that contain a mixture of painkilling ingredients, like aspirin, acetaminophen and caffeine mixtures in one pill.

- If you are taking analgesics, increase the amount of fluid you drink to six to eight glasses a day.

- If you are taking analgesics, avoid drinking alcohol

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- If you have kidney disease, consult your doctor before taking an analgesic, particularly NSAIDs and higher dose aspirin.

- Use NSAIDs under your doctor's supervision if you have heart disease, high blood pressure, kidney disease or liver disease or if you take diuretic medications or are over 65 years of age.

- Make sure your doctor knows about all medicines you are taking, even over-the-counter medicines.

- Make sure you read the warning label before using any over-the-counter analgesics.

Reference: https://www.kidney.org/atoz/content/painmeds_analgesics

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Supplement Use and Potential Kidney Damage (2013 study – Am J Kidney Disease)

The prevalence in the United States of dietary supplement use that may be harmful to those with chronic kidney disease (CKD) is unknown. We sought to characterize potentially harmful supplement use by individual CKD status.

Study Design

- Cross-sectional national survey (National Health and Nutrition Examination Survey, 1999-2008)

Setting & Participants

- Community-based survey of 21,169 non-pregnant, non-institutionalized U.S. civilian adults (≥20 years)

- Regardless, it is important to note that a substantial proportion of our study population reported taking supplements over many years, possibly placing themselves at risk of cumulative effects.

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- Consistent with this possibility, we found that individuals with CKD were more likely to report long-term supplement use than those with preserved kidney function.

- While we are unable to determine causality due to study design, this association highlights the need for further examination of the longitudinal relationship between supplement use and kidney function.

- In conclusion, the use of dietary supplements potentially harmful in the setting of CKD is common regardless of CKD status, even after accounting for confounders.

Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628413/

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Chronic kidney disease (CKD) = progressive loss in renal function over a period of months or years.

Early symptoms are non-specific, such as feeling generally unwell and reduced appetite.

Strongly linked to:

- Hypertension
- Diabetes - Diabetic nephropathy is the leading cause of chronic renal disease and a major cause of cardiovascular mortality.
- Cardiovascular disease
- Anemia – decrease EPO in CKD
- Pericarditis

- National Kidney Foundation (2002). Clinical practice guidelines for chronic kidney disease. http://www.kidney.org/professionals/KDOQI/guidelines_ckd

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Noteworthy Points

- **Diabetic nephropathy** is a common complication in type 1 and type 2 diabetes (20%–40% incidence among diabetics) and is one of the leading causes of end-stage renal disease (ESRD) in the US.

- **Diabetic retinopathy** is highly associated with nephropathy (60%–90% rate of comorbidity), and the absence of the retinopathy should increase suspicion that the nephropathy may have other causes

- **Cigarette smoking** is associated with proteinuria and quicker progression of all types of chronic kidney diseases

- **Target Blood Pressure** to prevent nephropathy or decrease progression of nephropathy <130/80 mmHg

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Incidence of CKD

- In Canada **1.9 to 2.3** million people have chronic kidney disease (about 6% of population)

- In the US, the Centers for Disease Control and Prevention found that CKD incidence was **16.8%** of adults aged 20 years and older, during 1999 to 2004.

- UK estimates suggest that **8.8%** of the population of Great Britain and Northern Ireland have symptomatic CKD.

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Causes of CKD

The most common causes of CKD are:

- Diabetes Mellitus
- Hypertension
- Glomerulonephritis – (NSAID's common cause)
- Autosomal Dominant Polycystic Kidney Disease
- Interstitial Nephritis

- **Diabetes, Hypertension and Glomerulonephritis** account for approximately 75% of all adult cases of CKD. Certain geographic areas have a high incidence of HIV nephropathy.

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Glomerulonephritis - inflammation of the glomeruli, or small blood vessels in the kidneys.

- Primary causes are intrinsic to the kidney.
- Secondary causes are associated with certain infections (bacterial – streptococcal glomerulonephritis, viral or parasitic pathogens), **drugs**, systemic disorders (SLE, autoimmune vasculitis), or **diabetes.**
- In our society drugs play an increasingly important role in kidney damage.
- Glomerulonephritis involves podocyte dysfunction (filtering cells with slits between) leading to proteinuria. **NSAIDs are major cause of glomerulonephritis.**

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Diagnosis Of CKD

- CKD often identified by high blood Creatinine.

- This indicates lower glomerular filtration rate (GFR) with lower capacity to filter end-products of metabolism from the body.

But, in early stages creatinine levels may be normal, and condition discovered upon Urinalysis:

- Positive microalbuminuria – earliest sign of CKD is detection of albumin in the urine (>30 mg/day but <300 mg/day); this is the microalbuminuria stage.

- The random spot urinary albumin-to-creatinine ratio is often used in diabetics and others at risk for CKD

- Overt nephropathy typically happens five to ten years after the onset of microalbuminuria and is characterized by persistent presence of albumin in the urine of >300mg/day and decline in kidney function as measured by glomerular filtration rate (GFR).

- And/Or Red Blood Cells present in urine (hematuria)

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Signs and Symptoms of Advancing CKD:

- **Blood pressure increased** due to fluid overload and production of vasoactive hormones created by the kidney via renin-angiotensin system. This also increases risk of **congestive heart failure**

- **Urea accumulates,** leading to azotemia and ultimately uremia (symptoms ranging from lethargy to pericarditis and encephalopathy).

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Azotemia is a medical condition characterized by abnormally high levels of nitrogen-containing compounds, such as urea, creatinine, various body waste compounds, and other nitrogen-rich compounds in the blood.

Signs and Symptoms of Azotemia include:

- Oliguria or anuria (decreased or absent urine output)
- Fatigue
- Asterixis (flapping tremor)
- Decreased alertness, Confusion
- Pale skin
- Tachycardia
- Xerostomia (dry mouth) and increased thirst
- Edema

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- **Uremic frost -**urea and urea derivatives secreted through the skin in sweat, which evaporates away to leave solid uric compounds, resembling a frost.

- **Hyperkalemia** – Potassium accumulates in the blood with range of symptoms including malaise and potentially fatal **cardiac arrhythmias**

- **Anemia** and fatigue from decreased synthesis of **Erythropoietin**

- **Fluid volume overload** — mild edema to life-threatening pulmonary edema

- **Hyperphosphatemia** — due to reduced phosphate excretion

- **Hypocalcemia** — due to 1,25 dihydroxyvitamin D_3 deficiency.

- Later this progresses to secondary hyperparathyroidism, renal osteodystrophy and vascular calcification that further **impairs cardiac function.**

- **Renal osteodystrophy** – usually **accompanies end-stage renal** disease begins. Blood tests indicate decreased calcium and calcitriol and increased phosphate and parathyroid hormone.

  X-rays show bone features of chondrocalcinosis (calcification in hyaline and/or fibrocartilage) at the knees and pubic symphysis, along with osteopenia and bone fractures.

- **Metabolic acidosis -** due to accumulation of sulfates, phosphates, uric acid other acid by-byproducts.

Symptoms of Metabolic Acidosis:

- Chest pain, palpitations
- Headache
- Altered mental status such as severe anxiety
- Decreased visual acuity
- Nausea, vomiting, abdominal pain
- Altered appetite (either loss of or increased)
- Then weight loss (longer term), muscle weakness and bone pains
- If left to progresses will lead to coma and death

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- **Cardiovascular Disease:** People with CKD suffer from **accelerated atherosclerosis** and are more likely to develop cardiovascular disease than the general population.

  Patients afflicted with CKD and CVD have significantly worse prognoses than those suffering only CVD

Imaging of Kidneys:

- In CKD Kidneys usually smaller (< 9 cm) than normal kidneys, with notable exceptions such as in diabetic nephropathy and polycystic kidney disease

- Additional tests may include nuclear medicine MAG3 scan to confirm blood flows and establish the differential function between the two kidneys

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Stages of CKD:

- All individuals with a GFR <60 mL/min/1.73 m^2 for 3 months are classified as having chronic kidney disease, irrespective of the presence or absence of kidney damage.

  This level or lower represents loss of half or more of the adult level of normal kidney function.

- Loss of protein in the urine regarded as an independent marker for worsening of renal function and cardiovascular disease.

Stage 1

- Slightly diminished function; kidney damage with normal or relatively high GFR (≥90 mL/min/1.73 m^2). Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

Stage 2

- Mild reduction in GFR (60–89 mL/min/1.73 m^2) with kidney damage. Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

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Stage 3

- Moderate reduction in GFR (30–59 mL/min/1.73 m^2).

Stage 4

- Severe reduction in GFR (15–29 mL/min/1.73 m^2)-- Preparation for renal replacement therapy

Stage 5

- End-stage Renal Disease (GFR <15 mL/min/1.73 m^2

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Who Should be Screened for CKD:

Subjects with:

- Hypertension
- History of CVD
- Diabetes
- Marked Obesity
- Everyone aged > 60 years
- Subjects with indigenous (native American Indian, First Nations) Racial Origin
- History of renal disease in the past (e.g. acute renal failure from idiosyncratic drug reaction or infection, stone obstruction, or flare up of autoimmune disease etc.)
- Relatives who had kidney disease requiring dialysis.

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Screening Tests:

- eGFR
- Serum Creatinine
- Urine - Albumin-to-Creatinine ratio in a first-morning urine specimen,
- as well as dipstick screen for Hematuria

When is Referral to Nephrologist Recommended:

- eGFR - less than 30 or decreasing by more than 3 mL/min/year
- Urine albumin-to-creatinine ratio is more than 30 mg/g
- Blood pressure difficult to control
- Hematuria or other findings suggest either a primarily glomerular disorder or secondary disease amenable to specific treatment

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Medical Treatment And Management Of CVD Risk Factors:

- CKD markedly increased risk of cardiovascular disease, and people with CKD often have other risk factors for heart disease, such as hyperlipidemia.

- **Most common cause of death in people with CKD is cardiovascular disease rather than renal failure**. Thus, aggressive treatment of hyperlipidemia is warranted.

- The leading cause of death in patients with chronic kidney disease is cardiovascular disease, *regardless of whether there is progression to stage* **5. Even patients in stage 5 die most often from cardiovascular events.**

- Patients with **end-stage** renal disease are also at increased overall **risk for cancer.** This risk is particularly high in younger patients and gradually diminishes with age

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Apart from controlling other risk factors, the goal of therapy is to slow down or halt the progression of CKD to stage 5. This usually includes:

- Control of blood pressure

- Treatment of the original disease, whenever feasible (discontinue offending drugs, manage autoimmune conditions, manage diabetes etc)

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Drugs For CKD:

- Usually ACE Inhibitors or ARBs – shown to slow the progression of CKD to stage 5. However patients still show disease progression on these drugs.

- Replacement of erythropoietin and calcitriol - often necessary in people with advanced disease. A target hemoglobin level of 9-12 g/dL is recommended

- Phosphate binders are also used to control the serum phosphate levels, which are usually elevated in advanced chronic kidney disease.

- Once in stage 5 CKD, renal replacement therapy is usually required, in the form of either **dialysis** or a **transplant**

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Understanding Drug-Induced Kidney Damage

- Drugs cause approximately 20 % of community-and hospital-acquired episodes of acute renal failure.

- Among older adults, the incidence of drug-induced nephrotoxicity may be as high as 66 %.

- Compared with 30 years ago, patients today are older, have a higher incidence of diabetes and cardiovascular disease, take multiple medications, and are exposed to more diagnostic and therapeutic procedures with the potential to harm kidney function (e.g. contrast dyes for kidney imaging and angiography testing).

- Drug-induced renal impairment is generally reversible, provided the nephrotoxicity is recognized early and the offending medication is discontinued

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Patients at highest risk of drug-induced nephrotoxicity are those with any of following:

- Age older than 60 years
- Baseline renal insufficiency (e.g., GFR < 60 mL per minute per 1.73 m2)
- Volume depletion
- Multiple exposures to nephrotoxins
- Diabetes
- Heart failure
- Sepsis
- Patients taking combination of drugs known to damage kidneys

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Highly Nephrotoxic Drugs:

- Certain drugs are inherently nephrotoxic and include aminoglycosides, amphotericin B (anti-fungal) cisplatin, contrast dye, and cyclosporine.

- Many other drugs can cause kidney damage over time, if taken on **a chronic basis** (e.g. NSAIDs)

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Types of Drug-induced Kidney Damage:

1. Alteration of intraglomerular hemodynamics (either afferent or efferent arteriole blood flow)
2. Tubular cell toxicity
3. Inflammation
4. Crystal nephropathy
5. Rhabdomyolysis
6. Thrombotic microangiopathy

We will examine each of these

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1. ALTERED INTRAGLOMERULAR HEMODYNAMICS

- In healthy state - approx. 120 mL of plasma is filtered by glomerulus per minute
- Kidneys **autoregulate intraglomerular pressure** by modulating afferent and efferent arterial tone to preserve GFR and urine output.
- In patients with volume depletion, renal perfusion depends **on circulating prostaglandins to vasodilate the afferent arterioles**, allowing more blood flow through the glomerulus.
- And action of **angiotensin-II–mediated vasoconstriction of the efferent arteriole.**
- Drugs with anti-prostaglandin activity **(e.g., NSAIDs)** or those with anti-angiotensin-II activity (e.g., **ACE inhibitors, ARBs**) can interfere with the kidneys' ability to autoregulate glomerular pressure and **decrease GFR. But ACE –inhibitors still used to slow kidney disease, ironically**

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2. TUBULAR CELL TOXICITY

- Renal tubular cells (especially proximal tubule cells), are vulnerable to the toxic effects of drugs due to role in concentrating and reabsorbing glomerular filtrate, which exposes them to high levels of circulating toxins.

Drugs that cause tubular cell toxicity do so by:

- impairing mitochondrial function
- interfering with tubular transport
- increasing oxidative stress or forming free radicals.

Drugs associated with this pathogenic mechanism of injury include:

- **Aminoglycosides (many different antibiotics),** amphotericin B (Fungizone; brand not available in the United States), antiretrovirals (adefovir [Hepsera], cidofovir [Vistide], tenofovir [Viread]), cisplatin (Platinol), contrast dye, foscarnet (Foscavir), and **zoledronate (Zometa).**

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3. INFLAMMATION (GLOMERULONEPHRITIS)

Some drugs cause inflammation of glomerulus, renal tubular cells, and the surrounding interstitium, leading to **fibrosis and renal scarring**.

- **Glomerulonephritis** is inflammation caused primarily by immune mechanisms and is often associated with **proteinuria** in the nephrotic range.

Medications exhibiting these effects include:

gold therapy, hydralazine (Apresoline; brand not available in the United States), interferon-alfa (Intron A), **lithium, NSAIDs**, propylthiouracil, and pamidronate (Aredia; in high doses or prolonged courses.

- **NSA**IDs also cause **tubulointerstitial nephritis** (inflammation in space between renal tubules.)

- **71-92%** of all cases caused by drugs (**Analgesics** and antibiotics such as methicillin).

- Other drugs, such as **calcineurin inhibitors** (e.g., cyclosporine [Neoral], tacrolimus [Prograf]), cause dose-dependent vasoconstriction of the afferent arterioles, leading to renal impairment in at-risk patients.

- **Calcineurin** normally stimulates T-cells in antigen-antibody activation, and is target of **immune suppressant drugs.**

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Chronic Renal Inflammation From Drugs:

- **Chronic interstitial nephritis** often caused by **acetaminophen, aspirin, and NSAIDs** when used chronically in high dosages (i.e., more than 1 gram daily for more than two years) or in patients with pre-existing kidney disease.

- Early recognition is important because chronic interstitial nephritis has been known to progress to end-stage renal disease.

- Diagnosis may be difficult because most patients do not consider over-the-counter preparations to be medications and tend to underreport frequency of use.

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Review of Common COX-inhibitor Anti-inflammatories with Anti-coagulant Effects:

1. Aspirin (ASA, bufferin, anacin, entrophen, robaxisal)
2. Diclofenac (voltaren)
3. Ibuprofen (advil and motrin)
4. Naproxen (aleeve)
5. Indomethacin (indocin)
6. Celebrex (celecoxib)

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Cause for Concern in the Use of Non-steroidal Anti-inflammatory Medications in the Community
A Population-Based Study
Robert J Adams; Sarah L Appleton; Tiffany K Gill; Anne W Taylor; David H Wilson; Catherine L Hill
Authors and Disclosures
Posted: 09/27/2011; BMC Family Practice. 2011;12(70)

- Non-steroidal anti-inflammation drugs (NSAIDs) are one of the most common causes of reported serious adverse reactions to drugs, with those involving the **upper gastrointestinal tract (GIT),[1] the cardiovascular system[2,3] and the kidneys being the most common**.[2,3] Much of the focus on NSAID adverse effects has been on GIT consequences, with good reason. A US study found the rate of deaths from NSAID-related GIT adverse effects is higher than that found from cervical cancer, asthma or malignant melanoma.[4]

- Significant deterioration in **blood pressure**,[5] development of chronic **heart failure** (CHF)[6] and serious cardiovascular events can also occur with a number of NSAIDs.[7] Risk is increased among the elderly and those with co-morbidities.[2,3] It has been suggested that the "burden of illness resulting from **NSAID-related CHF may exceed that resulting from GIT damage".[6]**

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- Recent evidence from a Danish population study suggests that cardiovascular mortality is increased among people without a prior history of cardiac disease by NSAIDs, particularly **diclofenac and ibuprofen**.[8] However, the baseline cardiovascular risk of people in this study was not reported.

- **NSAIDs are implicated in rapid deterioration of renal function**,[9,10] so national guidelines recommend the avoidance of nephrotoxic drugs (including NSAIDs) in people with chronic renal impairment.

See References on next slide

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National Kidney & Urologic Diseases
Information Clearinghouse (NKUDIC)
A service of the National Institute of Diabetes and Digestive and
Kidney Diseases , National Institutes of Health (NIH)

- **Kidney Disease From Acetaminophen and NSAIDs** - A form of kidney damage, called **analgesic nephropathy**, can result from taking painkillers every day for several years. Analgesic nephropathy is a chronic kidney disease that over years gradually leads to irreversible kidney failure and the permanent need for dialysis or a kidney transplant to restore kidney function. Researchers estimate that four out of 100,000 people will develop analgesic nephropathy. **It is most common in women over 30.**

- The painkiller phenacetin has been taken off the market because of its association with analgesic nephropathy. Recent studies have suggested that longstanding daily use of analgesics such as **acetaminophen or ibuprofen** may also increase the risk of chronic kidney damage, but this evidence is not as clear.

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Acute Renal Failure From Drugs:

- **Acute interstitial nephritis**, which can result from an allergic response to a suspected drug, develops in an idiosyncratic, non–dose-dependent fashion.

- Numerous drugs have been implicated, including allopurinol (Zyloprim); antibiotics (especially beta lactams, quinolones, rifampin [Rifadin], sulfonamides, and vancomycin [Vancocin]); antivirals (especially acyclovir [Zovirax] and indinavir [Crixivan]); diuretics (loops, thiazides); NSAIDs; phenytoin (Dilantin); proton pump inhibitors (especially omeprazole [Prilosec], pantoprazole [Protonix], and lansoprazole [Prevacid]); and ranitidine (Zantac).

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4. CRYSTAL NEPHROPATHY

Renal impairment may result from the use of drugs, foods or supplements that produce crystals that are insoluble in human urine. The crystals precipitate, usually within the distal tubular lumen, obstructing urine flow and eliciting an interstitial reaction.

Commonly implicated drugs include:

- antibiotics (e.g., ampicillin, ciprofloxacin [Cipro], sulfonamides)
- antivirals (e.g., acyclovir, foscarnet, ganciclovir [Cytovene])
- indinavir – anti-retroviral
- methotrexate
- Chemotherapy for lymphoproliferative disease, leading to **tumor lysis syndrome** with **uric acid** and calcium phosphate crystal deposition, has also been associated with renal failure.

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Other Factors Increasing Stone Formation

- Hypercalcemia secondary to excess Vitamin D – calcium phosphate deposition
- Large quantities of Vitamin C – in some people cause calcium oxalate stones as some Vitamin C is metabolized to oxalic acid
- Hyperuricemia increases stone formation as well. The following drugs promote hyperuricemia:
  - Alcohol
  - Thiazide diuretics
  - Cyclosporine
  - Furosemide
  - Cisplatin

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5. RHABDOMYOLYSIS

Rhabdomyolysis describes lysis of skeletal muscle cells, releasing intracellular myoglobin and creatine kinase into the plasma. Myoglobin induces renal injury secondary to direct toxicity, tubular obstruction, and alterations in GFR.

- Clinical manifestations of rhabdomyolysis include **weakness, myalgia, and tea-colored urine.**

- **Statins** are most recognizable agents associated with rhabdomyolysis,
- Recall that statins can also damage the liver, increase risk of diabetes or aggravate it, and in combination with fibrate drugs of niacin, there is greater risk of liver and kidney damage

- However, more than 150 medications and toxins can also increase risk of rhabdomyolysis

- Rhabdomyolysis with statin monotherapy is rare, with an average reported incidence of 0.44 per 10,000 person-years of therapy.

- Many drugs of abuse can also cause Rhabdomyolysis, such as **cocaine, heroin, ketamine (Ketalar), methadone, and methamphetamine.**

- **Drugs and alcohol cause 81% of rhabdomyolysis cases**, and up to 50 percent of patients subsequently develop acute renal failure.

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6. THROMBOTIC MICROANGIOPATHY

In thrombotic microangiopathy, damage caused by platelet thrombi in the microcirculation, as in thrombotic thrombocytopenic purpura (excess clotting disorder).

- Mechanisms of renal injury secondary to drug-induced thrombotic microangiopathy include an **immune-mediated reaction or direct endothelial toxicity.**

Drugs most often involved include:

- antiplatelet agents (e.g., **clopidogrel [Plavix], ticlopidine [Ticlid] – similar drug to Plavix)**
- cyclosporine
- mitomycin-C (Mutamycin)
- quinine (Qualaquin).

Systemic Lupus Erythematosus (SLE) – 10% of all cases of SLE are drug-induced, often involving nephritis. Most common drugs triggering SLE include:

- Procainamide – anti-arrhythmic drug
- Quinidine – anti-arrhythmic drug
- Hydralazine – used to treat severe hypertension, but usually in combination with beta-blocker to reflex sympathetic activity increasing heart rate contraction. Hydralazine relaxes arterial smooth muscle, decreasing resistance to blood flow.
- Isoniazid – antibiotic used to treat TB
- Methlydopa
- Chloropromazine –antipsychotic medication (i.e. schizophrenia)
- Propylthiouracil (anti-thyroid drug used in Grave's disease and other cases of hyperthyroidism)

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Pauci-immune Glomerulonephritis – vasculitis of kidney with minimal hypersensitivity characteristics and lack of antibody presence.

- Condition has been induced by following drugs:
- Propylthiouracil
- Penicillamine – chelating agent for copper (Wilson's disease)
- Infliximab (TNF- inhibitor used in autoimmune diseases)

- Chinese Herb known as Aristolochia fangchi has been shown to cause extensive kidney damage. The damaging agent is **aristolochic acid,** which may be present in other herbs as well.

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Additional Notes on NSAID's and Acetaminophen Kidney and Liver Damage

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Acetaminophen

- Safe dose of acetaminophen reported to be 4 grams daily
- But chronic daily ingestion of this dose has been shown to cause elevations of liver enzymes, even in healthy people (Watkins 2006).
- Since alcohol, especially when consumed chronically, augments the toxic potential of acetaminophen, many people unknowingly put themselves at risk of significant liver damage by consuming acetaminophen and alcohol together (Sharma 2009; van Mil 2001).
- Maximum recommended single dose is 1 gram and the maximum dose in a 24-hour period is 4 grams (Ferner 2011).

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Factors that can lower the threshold for overdose or increase the likelihood of liver failure include:

- ***Delays in treatment*** – the sooner treatment for overdose is begun, the better the chance of preventing liver failure and death

- ***Alcohol use*****.** Chronic alcohol use lowers the threshold for acetaminophen toxicity by induction of CYP enzymes and depletion of glutathione stores (Amar 2007).

- ***Medications*** - Anticonvulsants, antibiotics, antivirals, anti-gout, and anti-GERD treatments (proton pump inhibitors, H2 blockers) can increase the toxicity of an acetaminophen dose by induction of CYP enzymes, depletion of glutathione stores, or saturation of other liver detoxification systems (Amar 2007).

- ***Starvation and Malnutrition*****.** Starvation may deplete liver glutathione stores, as well as precursors for other acetaminophen detoxification pathways.

  Low dietary protein (a source of sulfur-containing amino acids used in glutathione synthesis) has been associated with increased sensitivity to acetaminophen toxicity in animals (Hwang 2009).

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- ***Age and Gender***. Acetaminophen toxicity is more common in women than men, is most common in people aged 30-40 years (Amar 2007).

- ***Genetics*.** Several mutations have been identified in the phase I and II detoxification genes required for acetaminophen metabolism, which may affect the rate of acetaminophen clearance or production of the toxic metabolite NAPQI (Zhao 2011).

- Any time acetaminophen is taken, at least 600 mg of N-acetyl cysteine should be taken along with it to help protect against liver toxicity.

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- In addition to standard liver enzyme tests, physicians should also measure blood levels of Cystatin C to look for signs of reduced kidney function in patients using acetaminophen

- Cystatin C has a low molecular weight and is removed from the bloodstream by glomerular filtration in the kidneys. If kidney function and glomerular filtration rate decline, the blood levels of cystatin C rise.

- Some reports suggest that serum levels of cystatin C are a more precise test of kidney function than serum creatinine levels

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Countering Acute Acetaminophen Overdose:

- Health care practitioners prescribe NAC either orally (1330 mg/kg of body weight, given over 72 hours - in my case 1,662.50mg per hr for 72 hrs) or intravenously (300 mg/kg of body weight, given over 20 hours) (Amar 2007).

- At these doses, the most common side effects of NAC are nausea and vomiting, although severe allergic reactions can occur in susceptible individuals (Ferner 2011).

- NAC should be given relatively quickly after an overdose, as its efficacy begins to decline 8-10 hours following intoxication (Smilkstein 1988; Buckley 2007). If administered within this window, however, NAC is very effective at mitigating toxicity.

- In a study of cancer patients taking high dose acetaminophen (an average dose of 400 mg/kg/day, up to a maximum of 1 gram/kg/day), a rescue dose of NAC within 8 hours of acetaminophen dosing prevented severe liver toxicity (Kobrinsky 1996).

- If taken within two hours of acetaminophen overdose, activated charcoal may absorb excess drug (Buckley 2007).

- Once acute liver failure has occurred or seems likely, however, the course of action is intensive supportive therapy or liver transplantation (Ferner 2011).

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NSAIDs

- ***NSAIDs*** are among the most widely used of all drugs, with 20 to 30 billion tablets sold each year in the U.S. alone (Peura 2002; Dal Pan 2009).

- COX-2 is normally inactive, but can be turned on during inflammation to produce pro-inflammatory prostaglandins.

- In contrast, COX-1 is normally active in many tissues, where it has roles unrelated to inflammation (e.g., clotting function in blood platelets, mucus production from cells lining the GI tract) (Toussaint 2010; Conaghan 2012).

- The inhibition of prostaglandins in the central nervous system also raises the pain threshold and acts on the hypothalamus to reduce body temperature (Amar 2007).

- Non-selective NSAIDs (aspirin, naproxen [e.g., Aleve®], ibuprofen [e.g., Advil®], diclofenac [e.g., Cambia®], and indomethacin [Indocin®]) inhibit the activity of both COX enzymes (Conaghan 2012).

- COX-2 selective NSAIDs (i.e., COX-2 inhibitors or coxibs) inhibit COX-2 more strongly than COX-1, resulting in less gastrointestinal side effects, but potential cardiovascular complications, most notably an increase in the risk of heart attack due to increased blood clotting propensity (Conaghan 2012).

- **NSAID Toxicity.** In contrast to the liver toxicity of acetaminophen, NSAIDs exhibit varying degrees of gastrointestinal, cardiovascular, and kidney toxicity.

- It should be noted that even non-selective NSAIDs have different degrees of selectivity toward COX-1 and COX-2 enzymes (Fitzgerald 2001).

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Adverse Effects of NSAID's

- **GI Effects**: Inhibition of COX-1 activity by non-selective NSAIDs (such as aspirin or ibuprofen) results in degradation of the protective mucus layer (Vonkeman 2010).

- Damage to the lining of the stomach and small intestine results in symptoms that range from relatively minor heartburn, nausea, and abdominal pain (affecting 15-40% of NSAID users) to the life-threatening ulceration, perforation, and bleeding (affecting 1-2% of chronic NSAID users) (Vonkeman 2010).

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- **CVD Risk:** Blood vessel endothelial cells produce an anti-clotting compound called prostaglandin I2 or PGI2. During blood vessel injury, the relative ratios of TXA2 (thromboxane made in platelets) and PGI2 are controlled by COX enzymes to balance the opposing actions of clotting and blood flow.

- COX-2 specific inhibitors (e.g., coxibs) preferentially reduce amounts of PGI2, tipping the balance toward thrombosis (Vonkeman 2010). The increased risk of thrombosis and heart attack observed in some studies of COX-2 inhibitors may result from this mechanism (Conaghan 2012).

- Increases in blood vessel constriction by COX-2 inhibition can also lead to the hypertension and renal failure seen in some studies of non-selective and COX-2 selective NSAIDs (Conaghan 2012).

- COX-2 inhibitors may also impair the removal of excess cholesterol from blood vessel walls, a process known as reverse cholesterol transport (Reiss 2009).

- COX-2 inhibitors can cause over production of two inflammatory and toxic cytokines, tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) (Takahashi 1998; Jeng 1995).

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- **Chronic Kidney Disease:** Long-term use of NSAIDs can lead to impaired glomerular filtration, renal tubular necrosis, and ultimately chronic renal failure by disrupting prostaglandin synthesis, which can impair renal blood flow (Weir 2002).

- This is because prostaglandins, which are blocked by COX inhibition, are important for proper blood vessel function within the kidneys (Ejaz 2004).

- Even in NSAID users with healthy kidneys, subclinical irregularities in kidney function are sometimes observed (Ejaz 2004). Other consequences of kidney toxicity related to NSAID use include high blood pressure, salt and water retention, and electrolyte imbalances (Ejaz 2004).

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- ***NSAIDs - Mitochondrial dysfunction and oxidative stress*.** NSAID's shown to promote mitochondrial dysfunction, thereby causing the formation of highly reactive free radicals. Free radicals cause tissue damage and may contribute to toxicity associated with NSAIDs (Sandoval-Acuña 2012; Patel 2012).

- This mechanism has been associated with NSAID-related gastrointestinal (Watanabe 2011) and liver toxicity (Doi 2010; O'Connor 2003). NSAIDs have also been shown to cause oxidative stress via a mitochondria-independent mechanism in vascular tissue (Li 2008).

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Several factors influence risk of NSAID Toxicity (Chen 2006; Vonkeman 2010):

- ***Age*.** Individuals over 60 are 5-6 times more likely to develop NSAID-related ulcers. Because older people generally have greater cardiovascular risk than younger people, their risk of NSAID-related cardiovascular events may also be elevated.

- ***Medical conditions*.** Prior history of ulcer or other gastrointestinal complications increase risk of NSAID ulcers 4- to 5-fold. Cardiovascular or respiratory disease, renal or hepatic impairment, diabetes, *Helicobacter pylori* infection, rheumatoid arthritis, and hypertension are also associated with increased risk. Individuals with cardiovascular risk factors such as hypertension, high cholesterol, or history of heart attack or bypass surgery are at increased risk of having an **NSAID-related cardiovascular event** (Conaghan 2012).

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- ***Dose and Duration of treatment*.** Use of high dose or multiple NSAIDs increase the risk of gastrointestinal complications up to 10-fold.

- Cardiovascular risk appears to increase in tandem with duration of NSAID use (Conaghan 2012).

- ***Medications*.** Simultaneous use of NSAIDs with corticosteroids, anticoagulants, aspirin, platelet inhibitors, and serotonin re-uptake inhibitors can increase gastrointestinal toxicity up to 15-fold.

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Nutritional Management in Kidney Disease

How strict the meal plan should be depends on the stage of kidney disease.

In the early stages of kidney disease, there may be little or no limits on what a patient can eat and drink.

As kidney disease gets worse, doctors may recommend patients limit:

- Potassium
- Phosphorus
- Fluids
- Sodium
- Diabetic nephropathy - LDL-cholesterol target is at or below 1.8 mmol/L (70 mg/dl) to prevent or slow further filtration deficits due to atherosclerosis (commonly seen in diabetes)

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Potassium

- When kidneys fail they can no longer remove excess potassium, so the level builds up causing hyperkalemia, which may occur in people with advanced stages of chronic kidney disease (CKD).

- Some of the effects of high potassium are nausea, weakness, numbness and slow pulse.

- Hyperkalemia is unpredictable and can be life-threatening. It can cause serious heart problems and sudden death. There are often no warning signs, meaning a person can have high potassium without knowing it. Thus, monitoring of blood potassium is required for patients with kidney disease.

- For people with stage 5 CKD (also known as end stage renal disease or ESRD), dialysis is necessary to help regulate potassium. Between dialysis treatments, however, potassium levels rise and high-potassium foods must be limited.

- Reference: https://www.kidney.org/atoz/content/hyperkalemia/facts

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Phosphorous

Normal working kidneys can remove extra phosphorus from the blood. With acute or chronic kidney disease (CKD), kidneys cannot remove phosphorus very well. High phosphorus levels can pull calcium out of your bones, making them weak. High phosphorus and calcium levels also lead to dangerous calcium deposits in blood vessels, lungs, eyes, and heart. The final result is vascular calcification that is frequently observed in CKD.

Experimental data have shown that phosphorus is involved in the whole process of vascular calcification leading to a new consensus that has renamed the old term of renal osteodystrophy with CKD mineral bone disorder (CKDMBD) and emphasizes the almost neglected role of the skeleton in these pathological states.

Paying attention to diet and medications for phosphorus control. Phosphorus can be found naturally in foods (organic phosphorus) and is naturally found in protein-rich foods such as meats, poultry, fish, nuts, beans and dairy products. Phosphorus found in animal foods is absorbed more easily than phosphorus found in plant foods.

Phosphorus additives found in foods include:

- Dicalcium phosphate
- Disodium phosphate
- Monosodium phosphate
- Phosphoric acid
- Sodium hexameta-phosphate
- Trisodium phosphate
- Sodium tripolyphosphate
- Tetrasodium pyrophosphate

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- Even relatively small elevations of serum phosphorus in the high normal range have been correlated in observational studies with increased cardiovascular and all cause mortality in patients with CKD, diabetes, coronary artery disease, or even normal adults.

- Phosphate load may be an important driver of vascular calcification, even in the absence of overt hyperphospahatemia.

Fibroblast Growth Factor23 (FGF23)

The main function of FGF23 seems to be regulation of phosphate concentration in plasma. FGF23 is secreted by osteocytes in response to elevated calcitriol. FGF23 acts on the kidneys, where it decreases the expression of NPT2, a sodium-phosphate cotransporter in the proximal tubule. Thus**, FGF23 decreases the reabsorption and increases excretion of phosphate**. **As such, FGF23 is usually secreted at high levels when too much phosphorous is present in the body (as it tries to excrete it).**

- High serum levels of Fibroblast Growth Factor23 (FGF23) have been associated with increased left ventricular mass, increased arterial stiffness, and more rapid decline of renal function, although its relation with vascular calcification remains rather conflicting.

- It should be noted that in all these studies the effect of FGF23 was independent of serum phosphate levels indicating that perhaps FGF23 is superior to serum phosphorus levels as a marker of morbidity or mortality in CKD patient

Reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3139680/

SEE COURSE NOTES FOR pdf. DOCUMENT SHOWING FOODS HIGH AND LOW IN SODIUM-POTASSIUM-PHOSPHOROUS – SOME EXAM QUESTIONS WILL BE GENERATED FROM THIS DOCUMENT

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Nutrition and Chronic Renal Failure: Conventional Management

References:

Current Therapy In Nutrition (KN Jeejeebhoy): 228-244. Decker Incorporated Publisher

Clinical Nutrition (2nd edition) (S. Halpern): 249-262. Lippincott Publisher

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Nutritional Therapy In RF:

1. Protein Requirements – as many **uremic toxins** are derived from protein metabolism protein **restriction is crucial** aspect of management of RF.

In kidney failure, urea and other waste products, which are normally excreted into the urine, are retained in the blood.

Early symptoms include anorexia and lethargy, and late symptoms can include decreased mental acuity and coma.

Usually diagnosed in patients when the glomerular filtration rate below 50% of normal

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Protein restriction very critical when GFR is below 20 ml/min

Protein - .55-0.6 gms protein/kg body wt/day

This normally keeps BUN below 80 mg/dL until reach end-stage disease

The protein sources should be high biological sources (egg white, chicken breast) and low in saturated fat and cholesterol. More recently vegetable proteins (soy) shown to be beneficial

2. Sodium Restriction – the ability to maintain sodium balance in CRF is remarkably well preserved, even in many cases of advanced disease (contrary to what we might expect).

However – sodium intake should not exceed 3500 mg (150 mEq) per day.

In more advanced disease it should be reduced to 500 – 1,000 mg/ (20-40 mEq) day

They often put patient on 2000 mg per day and monitor BP, body weight and peripheral edema and then increase or decrease sodium recommendations according to these parameters

3. Water – water balance is usually not a problem until the patient reaches end-stage RF. Can drink up to 3 Liters per day.

It is a misconception that volume of urine is an indicator of kidney function, or can improve kidney function.

Serum Creatinine and BUN are the indicators not urine volume.

Too much water intake in an attempt to flush the kidneys can result in hyponatremia, and so patients are counseled about increased water intake not improving kidney function

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4. Potassium – potassium restriction usually not required until end-stage with oliguria.

As they lower protein intake that naturally get less potassium anyway as a rule

Patients on dialysis must be careful with potassium foods to prevent hyperkalemia:

Citrus fruits

Tomatoes

Potatoes

Nuts

Beans

Chocolate

5. Phosphate (phosphorous) – retention of phosphate occurs *early in CRF,* but hyperphosphatemia is usually not seen until advanced stages of RF.

To Decrease Phosphourous Intake Patients advised initially to:

Restrict Protein

Restrict Dairy Products

With more advanced disease a greater number of foods must be avoided.

Sometimes intestinal phosphate-binding drugs are used to decrease phosphate absorption from gut (calcium carbonate with a aluminum-containing antacids – avoid magnesium-containing antacids as phosphate binders)

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6. Fat Intake – elevated triglycerides is common in CRF. With decreased protein intake patients consume more carbohydrates, which further exacerbates triglyceride elevation.

Patient must also maintain an LDL-cholesterol level at or below 1.8 mmol/L

Therefore: diet must be low in total protein, low in saturated fat and cholesterol, and low glycemic index with soluble fiber-containing carbs to slow carb absorption into blood (beans, peas, nuts, soy, oats, vegetables, fruits, low fat protein foods, olive oil, fish, avocadoes etc)

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7. Calcium – risk of calcium deficiency is high in CRF because:

- Decreased intestinal absorption of calcium
- Decreased blood levels of 1,25 dihydroxy vit D
- Decreased dairy intake

Calcium Supplementation recommended:

500 mg – 2,000 mg per day (more calcium required as creatinine levels rises and GFR is reduced). Calcium blood levels must be monitored as hypercalcemia can develop.

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8. Magnesium – hypermagnesemia is frequent in advanced CRF as kidney is primarily responsible of magnesium excretion and regulation.

Therefore, be careful with too much dietary magnesium (and supplements providing too much magnesium) and avoid use of magnesium-containing antacids and phosphate binders.

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9. Vitamin D – often reduced 1,25 dihydroxy vit D in blood (decreased renal synthesis),

Vitamin D supplementation (1,25 dihydroxy vit D) is often required to suppress parathyroid hormone secretion, which causes bone resorption of calcium to increase serum calcium levels and increase intestinal absorption of calcium (osteoporosis considerations)

- **Total Parenteral Nutrition** – beyond scope of course (as is Home Parenteral Nutrition and Home Enteral Nutrition) Refer to Pages 63-88 (Current Therapy In Nutrition (K. N.\Jeejeebhoy- B.C. Decker Inc 1988)

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Recent Studies Of Interest

- Involving CKD in patients with Diabetes
- If these dietary and supplementation practices help these high risk patients then should be extended to all patients with CKD

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Diabetic Diet and Supplements In Cases of CKD

Traditional Dietetic Management Includes:

- Blood glucose control (up to 65% of calories in diet throughout day)
- Protein restriction to 0.8–1.0g/kg/d (about 10% of daily calories) until more advanced kidney decline is seen
- Fat – about 25% of total daily calories
- Blood Pressure control, usually with ACE inhibitors and/or angiotensin II receptor antagonists.

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Faccini and Saylor Study in 2002

- A carbohydrate-restricted, low-dietary-iron, polyphenol-enriched diet (CR-LIPE) reduced death or renal transplant by nearly 50%, and reduced doubling of serum creatinine by half , compared to control group, in study of 191 subjects with type 2 diabetics with confirmed renal disease, and mean follow-up time of 3.9 years.

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Features of the CR-LIPE diet Compared to Diabetic Control Diet:

- approx 50% reduction of carbohydrates from the previous level of intake (35% vs 65%)
- higher protein intake – 25-30% vs 10% on standard dietetic regiment
- replacement of iron-rich red meats (beef and pork) with iron-poor white meats (poultry and fish) and with protein-enriched food items known to inhibit iron absorption, e.g., dairy, eggs, and **soy**
- fat intake slightly higher (30% vs 25%)
- elimination of all beverages except tea, water, red wine, and milk. Tea was highly recommended. Red wine was not to exceed 150 ml with lunch and 150 ml with dinner. Milk was recommended for breakfast. Outside mealtimes, water was the only approved beverage
- exclusive use of polyphenol-enriched extra-virgin olive oil for both dressing and frying
- except for carbohydrate restriction, ad libitum food consumption (up to the discretion of subjects).

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Postulated Benefits of Diet:

- Less iron intake and less iron absorption from binding with tannins (tea) polyphenols and milk. High amounts of iron induce oxidative stress damaging kidney cells. Less iron also shown to increase insulin sensitivity

- Low carbohydrate intake is also associated with a reduction in risk factors for morbidities associated with diabetes such as decreasing hyperlipidemia, insulinemia, and glycemia – these factors drive glomerulonephritis and glomerulosclerosis.

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Studies using soy protein in place of animal protein has shown benefit in reducing albuminuria:

- A small (n = 14), seven-month crossover study in male type 2 diabetics with nephropathy found soy-based diet significantly reduced urinary albumin excretion.

- Similar results in another small (n = 14), seven-week crossover study, showed replacement of portions of animal protein with soy and vegetable proteins, in a setting of a low-protein diet, reduced albuminuria and urinary urea nitrogen.

- A small (n = 12), 20-week crossover study of type 1 diabetics found that a soy-based diet significantly reduced GFR compared to control.

Reference: http://www.townsendletter.com/May2007/naturopathic0507.html

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- Substituting soy protein for animal proteins has been shown to improve or stabilize kidney function in several diabetic studies, including use of the vegetarian-based Portfolio Diet (reviewed in American Journal Of Clinical Nutrition: http://ajcn.nutrition.org/content/78/3/610S.full)

- A higher intake of fish protein is related to a lower risk of microalbuminuria in type 1 DM patients. The mechanisms involved in these findings are unknown but probably related to hemodynamic factors.

References:

Mollsten AV, Dahlquist GG, Stattin EL, Rudberg S: **Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type 1 diabetic patients.** *Diabetes Care* 2001, **24:**805-810.

Pecis M, de Azevedo MJ, Gross JL: **Chicken and fish diet reduces glomerular hyperfiltration in IDDM patients.** *Diabetes Care* 1994, **17:**665-672.

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- Substituting chicken for red meat reduced urinary albumin excretion, and also the serum levels of total cholesterol, LDL and apolipoprotein B in patients with type 2 DM and micro and macroalbuminuria.

- Also showed that positive effect on renal function was similar to use of enalapril (ACE –inhibitor drug) for a 12-month period in patients with type 2 DM

Reference:

http://www.dmsjournal.com/content/1/1/10 (Diabetology and Metabolic Syndrome 2009)

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Supplements Shown To Improve Diabetic Nephropathy and/or CKD

1. **Antioxidants** - evidence shows free radical damage is major unifying factor in kidney cell damage, and micro and macrovascular damage seen in diabetic nephropathy and in many cases of drug-induced nephropathies.

- Supplementation with various antioxidants has been shown to improve kidney function in various studies

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References – Antioxidants and CKD

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Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. *Diabetes Care.* 1996 Mar;19(3):257–267.

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Sundaram RK, Bhaskar A, Vijayalingam S, Viswanathan M, Mohan R, Shanmugasundaram KR. Antioxidant status and lipid peroxidation in type II diabetes mellitus with and without complications. *Clin Sci* (London). 1996 Apr;90:255–260.

Hirsch IB, Atchley DH, Tsai E, Labbe RF, Chait A. Ascorbic acid clearance in diabetic nephropathy. *J Diabetes Complications*. 1998 Sep–Oct;12(5):259–263.

Maxwell SRJ, Thomason H, Sandler D, et al. Antioxidant status in patients with uncomplicated insulin-dependent and non-insulin-dependent diabetes mellitus. *Eur J Clin Invest.* 1997; 27:484–490.

Hartnett ME, Stratton RD, Browne RW, Rosner BA, Lanham RJ, Armstrong D. Serum markers for oxidative stress and severity of diabetic retinopathy. *Diabetes Care*. 2000;23:234–240.

Uchimura K, Nagasaka A, Hayashi R, et al. Changes in superoxide dismutase activities and concentrations and myeloperoxidase activities in leukocytes from patients with diabetes mellitus. *J Diabetes Complications*. 1999;13:264–270.

Salonen JT, Nyyssonen K, Tuomainen TP, et al. Increased risk of non-insulin dependent diabetes mellitus at low plasma vitamin E concentrations: A four-year follow-up study in men. *BMJ*. 1995;311:1124–1127..

Opara EC, Abdel-Rahman E, Soliman S, et al. Depletion of total antioxidant capacity in type 2 diabetes. *Metabolism* 1999;48:1414–1417.

Shigeta Y, Hiraizumi G, Wada M, Oji K, Yoshida T. Study on the serum level of thioctic acid in patients with various diseases. *J Vitaminol* (Kyoto). 1961;7:48–52.

Packer L, Witt EH, Tritschler HJ. Alpha-lipoic acid as a biological antioxidant. *Free Radic Biol Med*. 1995;19:227–250.

Brownlee M. The pathobiology of diabetic complications: A unifying mechanism. *Diabetes.* 2005 Jun;54(6):1615–1625.

Beisswenger PJ, Drummond KS, Nelson RG, Howell SK, Szwergold BS, Mauer M. Susceptibility to diabeticnephropathy is related to dicarbonyl and oxidative stress. *Diabetes.* 2005 Nov;54(11):3274–3281.

Brenner BM. Regarding: "Management of glomerular proteinuria: a commentary." *J Am Soc Nephrol*. 2004 May;15(5):1354–1357.

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Antioxidant Studies Using Vitamin C and Vitamin E

Clinical studies have shown significantly reduced urinary albumin excretion in diabetics with:

- Vitamins C (200 mg) and E (100 IU) for 12 weeks
- or Vitamins C (1,250 mg) and E (680 IU) for four weeks
- or Vitamin E (1200 IU) for four months, or vitamin C (500, twice daily.) for nine months

- **References:**
- Farvid MS, Jalali M, Siassi F, Hosseini M. Comparison of the effects of vitamins and/or mineral supplementation on glomerular and tubular dysfunction in type 2 diabetes. *Diabetes Care*. 2005 Oct;28(10):2458–2464.
Gaede P, Poulsen HE, Parving HH, Pedersen O. Double-blind, randomised study of the effect of combined treatment with vitamin C and E on albuminuria in type 2 diabetic patients. *Diabet Med.* 2001 Sep;18(9):756–760.
Hirnerova E, Krahulec B, Strbova L, Stecova A, Dekret J, Hajovska A. Effect of vitamin E therapy on progression of diabetic nephropathy *Vnitr Lek.* 2003 Jul;49(7):529–534.
McAuliffe AV, Brooks BA, Fisher EJ, Molyneaux LM, Yue DK. Administration of ascorbic acid and an aldose reductase inhibitor (tolrestat) in diabetes: Effect on urinary albumin excretion. *Nephron*. 1998 Nov;80(3):277–284.

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Zinc and Magnesium

- Addition of daily **zinc (30 mg), magnesium (200 mg**) to vitamins C **(200 mg)** and **E (100 IU)** therapy resulted in a synergistic reduction of urinary albumin excretion

Reference:(http://care.diabetesjournals.org/content/28/10/2458.full.pdf)

So , be on guard for signs of magnesium deficiency, which can occur if over restrict magnesium:

Tics, muscle spasms and cramps, seizures, anxiety, and irregular heart rhythms

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Alpha-Lipoic Acid

- **Alpha-lipoic acid** (600 mg) supplementation in type 1 and type 2 diabetics for 18 months halted progression of urinary albumin concentration (UAC), compared with controls whose UAC nearly doubled.

- This dose of alpha-lipoic acid has been shown to exert significant antioxidant activity even in the setting of poor glycemic control and a wide range of albuminuria.

References:

- Morcos M, Borcea V, Isermann B, et al. Effect of alpha-lipoic acid on the progression of endothelial cell damage and albuminuria in patients with diabetes mellitus: An exploratory study. *Diabetes Res Clin Pract.* 2001 Jun;52(3):175–183.
  Borcea V, Nourooz-Zadeh J, Wolff SP, et al. Alpha-lipoic acid decreases oxidative stress even in diabetic patients with poor glycemic control and albuminuria. *Free Radic Biol Med*. 1999 Jun;26(11–12):1495–1500.

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- Alpha lipoic acid supplementation also shown to help **reverse diabetic neuropathy**

Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: A meta-analysis. *Diabet Med.* 2004 Feb;21(2):114–121. 64.

Ziegler D, Ametov A, Barinov A et al. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: The SYDNEY 2 trial. *Diabetes Care*. 2006 Nov;29(11):2365–2370.

- A three-month trial comparing **alpha-lipoic acid** (600 mg) or **selenium (100 mcg) or d-alpha-tocopherol** (1200 IU), with a control group, found significantly diminished urinary albumin excretion rates in each of the three antioxidant groups.

Kahler W, Kuklinski B, Ruhlmann C, Plotz C. Diabetes mellitus – a free radical-associated disease. Results of adjuvant antioxidant supplementation. [In German.] *Z Gesamte Inn Med.* 1993 May;48(5):223–32

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N-Actetylcysteine

- NAC used in patients with pre-existing kidney damage to prevent further kidney damage resulting from dye that is used in tests such as angiograms (dye studies).

Reference: C:\Users\Toshiba\Desktop\Articles to print\A Study of The Effectiveness of N-Acetylcysteine in Kidney Protection Following Cardiopulmonary Bypass - Full Text View - ClinicalTrials_gov.mht

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NAC Intravenous Studies

- Testing to see if NAC can help protect kidneys from damage caused by heart-lung machine during cardiac surgery.

- Kidney damage often occurs in patients undergoing cardiac surgery requiring use of heart-lung machine. Kidney failure after surgery is a serious complication (2-30% of patients with kidney problems can develop it) and it can lead to short term and long-term dialysis, as well as death (there is up to a 30% death rate once kidney failure develops).

- However, 3% to 6% of people given intravenous acetylcysteine show a severe, anaphylaxis-like allergic reaction, which may include extreme breathing difficulty (due to bronchospasm), a decrease in blood pressure, rash, angioedema, and sometimes also nausea and vomiting

- **Reference:** C:\Users\Toshiba\Desktop\Articles to print\A Study of The Effectiveness of N-Acetylcysteine in Kidney Protection Following Cardiopulmonary Bypass - Full Text View - ClinicalTrials_gov.mht

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Astragalus

- Preliminary studies show positive effects of astragalus on repairing liver and kidney damage (http://www.umm.edu/altmed/articles/astragalus-000223.htm)

- I like astragalus with reishi mushroom, as both also repair liver damage and modulate immune function (http://www.idosi.org/aejb/1(3)08/8.pdf)

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- 3-month study using Fructus Arctii and Radix Astragalus showed significantly reduced urinary albumin excretion in individuals with diabetic nephropathy.

- A decoction of Radix Astragalus and Rhizoma Ligustici Chuanxiong (150 ml once pe day.) for six months significantly decreased urinary albumin excretion in type 2 diabetic individuals with microalbuminuria

- Wang HY, Chen YP. Clinical observation on treatment of diabetic nephropathy with compound fructus arctii mixture. [In Chinese.] *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 2004 Jul;24(7):589–592.
- Lu ZM, Yu YR, Tang H, Zhang XX. The protective effects of Radix Astragali and Rhizoma Ligustici chuanxiong on endothelial dysfunction in type 2 diabetic patients with microalbuminuria. [In Chinese.] *Sichuan Da Xue Xue Bao Yi Xue Ban*. 2005 Jul;36(4):529–532

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Animal Studies With Polyphenols, Quercetin and Curcumin

- Animal studies show polyphenols reduce transforming growth factor-beta and prevent fibrosis and deterioration of renal function, and reduce uremic end- products in renal failure.

- Quercetin and turmeric (Curcumin) have been shown to attenuate the severity of nephropathy

References:

Shi SH, Zheng SS, Jia CK, Zhu YF, Xie HY. Inhibitory effect of tea polyphenols on transforming growth factor-beta1 expression in rat with cyclosporine A-induced chronic nephrotoxicity. *Acta Pharmacol Sin*. 2004 Jan;25(1):98–103.

Yokozawa T, Cho EJ, Nakagawa T. Influence of green tea polyphenol in rats with arginine-induced renal failure. *J Agric Food Chem*. 2003 Apr 9;51(8):2421–2425.

Anjaneyulu M, Chopra K. Quercetin, an anti-oxidant bioflavonoid, attenuates diabetic nephropathy in rats. *Clin Exp Pharmacol Physiol.* 2004 Apr;31(4):244–248.

Tirkey N, Kaur G, Vij G, Chopra K. Curcumin, a diferuloylmethane, attenuates cyclosporine-induced renal dysfunction and oxidative stress in rat kidneys. *BMC Pharmacol.* 2005 Oct 15;5:15.

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Omega-3 Fat Supplementation

- Several clinical studies showed eicosapentaenoic omega-3 fatty acids (EPA) improved urinary albumin excretion ratios for type 2 diabetics at 900 mg/day and 1,800 mg/day doses

- Other supplementation studies show improving omega-3:omega-6 ratio also reverses diabetic nephropathy (converting macro to microalbuminuria, and sometimes to microalbuminuria).

References:

Shimizu H, Ohtani K, Tanaka Y, Sato N, Mori M, Shimomura Y. Long-term effect of eicosapentaenoic acid ethyl (EPA-E) on albuminuria of non-insulin dependent diabetic patients. *Diabetes Res Clin Pract.* 1995 Apr;28(1):35–40.

Hamazaki T, Takazakura E, Osawa K, Urakaze M, Yano S. Reduction in microalbuminuria in diabetics by eicosapentaenoic acid ethyl ester. *Lipids.* 1990 Sep;25(9):541–545.

- Cardenas C et al. Polyunsaturated fatty acid consumption may play a role in the onset and regression of microalbuminuria in well-controlled type 1 and type 2 diabetic people: A 7-year, prospective, population-based, observational multicenter study. *Diabetes Care*. 2004 Jun;27(6):1454–1457.

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GLA and ALA

- **Gamma-linolenic acid** – dose of 480 mg/day or 500 mg from borage seed oil shown to improve diabetic Neuropathy

(http://www.bioriginal.com/services/files/file_13.pdf)

- **Alpha-linolenic acid** – overall studies support supplementation use in primary and secondary prevention of vascular disease, common in CKD - 1-3 gm per day

(http://www.ncbi.nlm.nih.gov/pubmed/15945135)

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Gum Arabic

- Gum Arabic (GA) - fermentable carbohydrate derived from the dried exudates of *Acacia senegal*
- Widely used in both the pharmaceutical and food industries as an emulsifier and stabilizer
- In Sudan particularly, GA used to **ameliorate the severity of CRF**, and has been shown to **reduce the frequency of dialysis** from three to two times per week.
- Treatment with GA has been claimed to result in a urea-lowering effect by increasing fecal urea nitrogen excretion, with a concomitant decrease in urinary total nitrogen in adults and children.

References: Badreldin H Ali. Effects of Gum Arabic in rats with adenine-induced chronic renal failure. *Exp Biol Med* March 2010 vol. 235 *no. 3 373-382*

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- GA also shows strong antioxidant properties (http://cdn.intechopen.com/pdfs/31731/InTech-Gum_arabic_more_than_an_edible_emulsifier.pdf)

- GA shows evidence of modest reductions in blood glucose and cholesterol, attributable to soluble fiber content (viscous fiber)

- **Dosage**: 15-25 gm per day

- Verification of GA positive effects on human kidney function awaits requires further studies, according to most authorities

- (http://faculty.ksu.edu.sa/18856/Articles/Biological%20effects%20of%20gum%20arabic%20A%20review%20of%20some%20recent%20research.pdf)

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Oxidative Stress and Antioxidants In CKD: Life Extension

http://www.lifeextension.com/Protocols/Kidney-Urinary/Kidney-Disease/Page-04

- Different mechanisms could explain the increased oxidative stress in CKD.

- Basic characteristics of renal patients such as advanced age, diabetes, renal hypertension, lower levels of antioxidant vitamin due to dietary restriction of fresh fruits and vegetables (to avoid hyperkalemia), and failure of ROS clearance with decline in renal function are implicated in increased oxidative stress and progression of CKD; and oxidative stress seems to happen early during the course of renal decline.

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Antioxidants Cited by Life Extension Review

CoQ10

- Animal studies have shown that CoQ10 can protect kidney tissue from numerous nephrotoxic drugs, including gentamicin, a powerful antibiotic with a notorious propensity for causing kidney damage (Farswan 2005; Upaganlawar 2006).

- These findings are significant not only because they offer protection in patients who might be exposed to such drugs, but they teach us about CoQ10's potent ability to combat the extreme oxidant stress that the kidney faces as it deals with a variety of foreign chemicals.

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Silymarin

- Mushroom poisons (mycotoxins) are among the most deadly natural toxins known. Their kidney toxicity is surpassed only by some of the most aggressive chemotherapy agents. Physicians have therefore looked to silymarin as a potential “renoprotective” agent for patients undergoing chemotherapy.

- Silymarin is also protective against several classes of nephrotoxic drugs, in particular cisplatin and Adriamycin®, two of the most potent and damaging (owing to oxidative damage and severe inflammation) chemotherapeutic drugs (Launay-Vacher 2008; Machado 2008; Yao 2007).

- Researchers around the world have found that silymarin and its components reduce and often prevent the kidney damage caused by these drugs (Bokemeyer 1996; Gaedeke 1996; Karimi 2005; El-Shitany 2008).

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- Silymarin's ability to protect against the oxidative stress produced by potent drugs suggests that it may be useful in protecting against more subtle, chronic injury by free radicals -- particularly those generated by chronic blood glucose elevations.

- German researchers, for instance, have found that silymarin could prevent injury to renal cells incubated with elevated glucose concentrations while blocking production of oxidative stress markers (Wenzel 1996).

- Silymarin's protective power also extends to ischemia/reperfusion injury (restoration of blood supply following restriction of blood flow). Turkish researchers demonstrated that by pre-treating animals with silymarin, they could completely prevent visible and functional damage to kidney structures exposed to this kind of injury (Senturk 2008; Turgut 2008).

- Studies such as these suggest that by maintaining optimal antioxidant function through supplementation, we may be able to prevent much (if not most) of the chronic oxidative damage to which our kidneys are exposed on a daily basis. As a result, they have huge implications for the general population.

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Resveratrol

- Resveratrol, due to its antioxidant and anti-inflammatory potential, has been utilized in studies to prevent drug-induced kidney damage. The following results were noted when rats, exposed to antibiotic gentamicin, were treated with resveratrol: 1) nephrotoxicity was significantly reduced, 2) more rapid healing of injured kidney tissue was attained, and 3) a dramatic reduction in markers of oxidant injury was observed (Silan 2007).

- A team of toxicologists in Brazil demonstrated its protective power against cisplatin, the powerful chemotherapy agent responsible for so much drug-induced kidney damage (Do Amaral 2008). Finally, Indian pharmacologists were successful in protecting animal kidneys from damage caused by cyclosporine A (another common chemotherapy and immune suppressant drug) by pre-treating the animals with resveratrol (Chander 2005).

- Since diabetes is the leading cause of kidney disease—and because the damage it inflicts is largely mediated by free radical production resulting from destructive alteration of proteins by glucose (glycation)—researchers have explored resveratrol as a preventive in diabetic kidney damage.

- Promising results have come from Indian pharmacologists who significantly attenuated kidney damage in rats with experimentally induced diabetes, even 4 weeks after the diabetes was induced (Sharma 2006).

- In the researchers' own words, "The present study reinforces the important role of oxidative stress in diabetic kidney disease and points towards the possible antioxidative mechanism being responsible for the renoprotective action of resveratrol."

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Alpha Lipoic Acid

- Lipoic acid has been comprehensively studied worldwide for its power to prevent or mitigate drug-induced kidney damage.

- We know that lipoic acid is an effective kidney-protective agent against damage inflicted by Adriamycin® (Malarkodi 2003), the immunosuppressive drug cyclosporine A (Amudha 2006; Amudha 2007(a,b)), and even against acute toxic doses of the pain reliever acetaminophen (Abdel-Zaher 2008). In studies examining the protective benefits of lipoic acid against cyclosporine toxicity, it helped to normalize blood lipid abnormalities (Amudha 2007).

- Nephrologists at Georgetown University examined lipoic acid in the context of diabetic kidney disease. Their results showed that it can improve renal function in diabetes by lowering sugar levels (Bhatti 2005).

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- They also demonstrated that lipoic acid lowers protein loss in urine and improves kidney structure and function by reducing oxidative stress in diabetic laboratory animals (Bhatti 2005).

- In yet another compelling study, Korean researchers showed that they could improve kidney patients' responses to the vasodilator (blood vessel relaxer) nitric oxide (NO) by supplementing them with lipoic acid (Chang 2007). Loss of endothelial responsiveness to NO is a cause of vascular disease in diabetics.

- A chemical called asymmetric dimethylarginine (ADMA) is a sensitive marker and predictor of cardiovascular outcome in patients with end-stage renal disease. Fifty patients on hemodialysis were treated with 600 mg lipoic acid daily for 12 weeks. ADMA levels remained unchanged in the control group but fell significantly in the treatment group, suggesting that lipoic acid may reduce the risk of cardiovascular complications in this group of patients.

Reference: Life Extension: http://www.lifeextension.com/Protocols/Kidney-Urinary/Kidney-Disease/Page-04

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NAC and Contrast Dye Protection

- N-acetylcysteine (NAC) is commonly used for the prevention of radiocontrast induced nephropathy (RCIN) despite inconsistent results from numerous clinical trials and meta-analyses. While most research has been carried out using a specific oral dosage regimen, the intravenous route allows more rapid administration and may be particularly advantageous for urgent procedures such as coronary angiography. However, pharmacokinetic studies and clinical trial evidence suggest that the dose and route of administration are key factors in determining the therapeutic effectiveness of NAC for this indication.

- The exact mechanism by which NAC may prevent RCIN is unknown, although antioxidant and vasodilatory effects likely play a key role. NAC directly scavenges oxygen free radicals, and also serves as a precursor of glutathione, itself a natural antioxidant.

- In addition, NAC increases the concentrations of both nitric oxide, a potent but short acting vasodilator, and S-nitrosothiol, which has more prolonged vasodilatory effects.

- The use of NAC for the prevention of RCIN gained widespread interest after a study by Tepel and colleagues demonstrated that the incidence of RCIN after radiocontrast enhanced computed tomographic (CT) scanning was significantly reduced by oral NAC administration compared to placebo.

- Many clinical trials followed, particularly in the setting of cardiac catheterisation. Results from these trials have been inconsistent, prompting several meta-analyses, which themselves have produced conflicting results.

- Results from clinical trials evaluating the effectiveness of NAC for preventing RCIN have been remarkably inconsistent. Variable results from studies utilising the oral NAC protocol introduced by Tepel and colleagues may be at least partially explained by the wide range of products studied, and some evidence supports the use of higher doses.

- A single 500 mg intravenous bolus is insufficient. One study supports the use of a much higher intravenous dose, equivalent to that used for paracetamol overdose, although questions regarding study design prevent these findings from being considered definitive.

- Importantly, all trials conducted to date, including our own, have relied on serum creatinine as a surrogate marker for glomerular filtration rate and NAC itself appears to directly lower creatinine concentrations.

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- Furthermore, there is little evidence that any studied dosage regimen reduces RCIN associated morbidity or mortality. A large dose ranging study utilising creatinine independent estimates of glomerular filtration rate and clinical end points is warranted.

- In the meantime, although it is likely that NAC will continue to be utilised for this indication since it appears to be safe and inexpensive at low doses, clinicians should be aware of the uncertainties concerning its effectiveness. Whether or not NAC is administered by any route, other strategies for preventing RCIN should be employed including adequate hydration with isotonic saline or bicarbonate solutions, avoidance of potentially nephrotoxic medication, and the use of minimal amounts of appropriate radiocontrast media.

NAC Reference:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1769030/

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Conclusion

Many of the same supplements used to mitigate and reverse liver damage, also help preserve, slow, and sometimes reverse kidney function.

Key Supplements:

- Vitamin C – be careful in kidney stones patients (750 mg max)
- Vitamin E
- Alpha-lipoic acid
- NAC
- Astragalus
- Curcumin
- Quercetin
- Essential Fatty Acids
- Gum Arabic – also lowers glucose and cholesterol via soluble fiber content.
- Betaine (L-Taurine)

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Supplements Protocol Considered in CKD Patients In Early-Moderate Stage

- High Potency Multiple Vitamin (antioxidant-enriched, magnesium, zinc)
- Ultimate GLX (NAC, ALA, Silymarin, L-glutamine) – I have seen lower creatinine in autoimmune cases
- Lecithin – (1200 mg capsules) – 2x per day – some choline oxidized to Betaine (may also add L-Taurine -1,000-2,000 mg)- Osmoprotectants
- Milk Thistle (90-95% Silymarin Content)
- Curcumin – 400 mg, twice daily
- Quercetin – 100-200 mg, 1-2x daily
- Astragalus -250 – 500 mg (10:1 extract) per day https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0069179/
- http://www.raysahelian.com/astragalus.html
- Essential Fatty Acids (i.e. fish, flaxseed and borage)
- CoQ10 – 60-100 mg/d
- Possibly Gum Arabic

Kidney monitoring required in all cases of supplement use in patients with any stage of CKD. No supplements should be given to patients in a state of acute kidney failure or decline.(i.e. acute onset ANCA Vasculitis of kidneys)

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Reducing Kidney Drug-Damage Effects Over Lifetime

Try to eliminate or reduce dosage of known kidney-damaging drugs with non-kidney damaging alternatives:

Examples:

1. **Analgesics/Anti-inflammatory Drugs** – Natural anti-inflammatories and/or California poppy, alternative manual and electrotherapies
2. **Statin Drugs –** diet, exercise, supplements (although statin drugs have shown promise in mitigating oxidative damage to kidneys in CKD)
3. **Bisphosphanate Drugs** – therapeutic doses of calcium, Vitamin D, magnesium, icariin flavonoid, exercise etc

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Other Serious Kidney Conditions

Hereditary Conditions Affecting the Kidneys

- Polycystic Kidney Disease
- Hereditary Nephritis
- Hemochromatosis
- Diabetes Insipidus

Autoimmune Conditions Affecting the Kidneys

- Goodpasture's Syndrome
- Lupus
- ANCA Vasculitis
- Wegener's Granulomatosis
- IgA Nephropathy

Infection-Related Glomerular Disease

- Acute Streptococcal Glomerulonephritis
- Bacterial Endocarditis
- HIV-Infection

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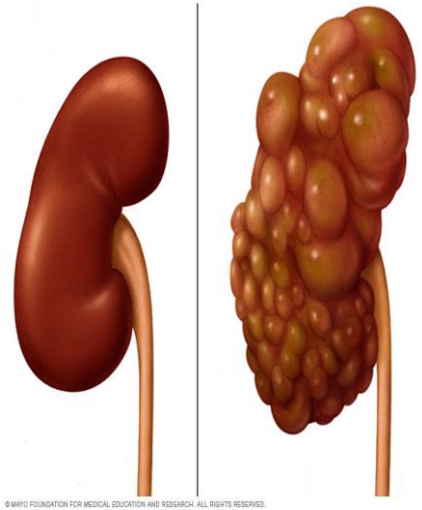
Hereditary Conditions:

1. Polycystic Kidney Disease - Polycystic kidney disease (PKD) is an inherited disorder in which clusters of cysts develop primarily within your kidneys, causing your kidneys to enlarge and lose function over time. Cysts are noncancerous round sacs containing fluid. The cysts vary in size, and they can grow very large. Having many cysts or large cysts can damage your kidneys.



- Polycystic kidney disease also can cause cysts to develop in the liver and elsewhere in the body. The disease can cause serious complications, including high blood pressure and kidney failure.
- PKD varies greatly in its severity, and some complications are preventable.
- **Prognosis**. By age 75, 50 to 75% of patients with ADPKD require renal replacement therapy (dialysis or transplantation)
- The earlier the age of onset the worse the prognosis usually.

There are no studies showing that supplementation can be helpful in slowing the progression of PKD. This is a condition best treated by the Nephrologist and Dietician.

Reference: https://www.mayoclinic.org/diseases-conditions/polycystic-kidney-disease/symptoms-causes/syc-20352820

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2. Hereditary Nephritis—Alport Syndrome

- The primary indicator of Alport syndrome is a family history of chronic glomerular disease, although it may also involve **hearing or vision impairment.**
- This syndrome affects both men and women, but men are more likely to experience chronic kidney disease and sensory loss.
- Men with Alport syndrome usually first show evidence of renal insufficiency while in their twenties and **reach total kidney failure by age 40.**
- Women rarely have significant renal impairment, and hearing loss may be so slight that it can be detected only through testing with special equipment.
- Usually men can pass the disease only to their daughters. Women can transmit the disease to either their sons or their daughters.
- Treatment focuses on controlling blood pressure to maintain kidney function.

Reference: https://www.niddk.nih.gov/health-information/kidney-disease/glomerular-diseases

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3. Hemochromatosis: This is an iron overload condition, whereby the gut allows too much iron to be absorbed into the bloodstream – usually stored in excess in liver.

- It is suspected in males and postmenopausal females upon the discovery of a serum ferritin value of over 300 ng/mL (670 pmol/L).
- In premenopausal females, a serum ferritin value of over 150 or 200 ng/mL (330 or 440 pmol/L) indicates iron overload.
- A simple blood test (HFE) confirms the diagnosis of hereditary hemochromatosis
- The iron overload usually damages the live over time, leading to liver failure if preventive measures are not put into place.
- Periodic Venesection (or blood letting) helps to keep serum ferritin within the safe and ideal range.

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- On rare occasions hemochromatosis can damage kidney cells before any signs of liver damage.

- As such, treatment for hemochromatosis may also help prevent decline in kidney function.

- Patients with end-stage renal disease usually need iron and erythropoietin substitution to prevent renal anaemia. The target haemoglobin level is 110–130 g/l and target ferritin level is usually >200 ng/ml, according to international guidelines.

- However, in patients with iron storage diseases such as hereditary haemochromatosis (HH), iron substitution is contra-indicated and ferritin levels, in general, should be <50 ng/ml to prevent secondary organ damage.

Reference: https://academic.oup.com/ckj/article/2/1/43/451583

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4. Diabetes Insipidus - a condition characterized by large amounts of dilute urine and increased thirst. The amount of urine produced can be nearly 20 liters per day. Reduction of fluid has little effect on the concentration of the urine. Complications may include dehydration or seizures.

- It is usually caused by lack of vasopressin (anti-diuretic hormone), from damage to hypothalamus, pituitary or genetic causes, or failure to respond to vasopressin.

- About 3 in 100,000 people develop this condition. It requires management from a Nephrologist and Dietician

Reference: https://web.archive.org/web/20170513120920/https://www.niddk.nih.gov/health-information/kidney-disease/diabetes-insipidus

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Autoimmune Diseases Affecting Kidneys:

1. Goodpasture's Syndrome - involves an autoantibody that specifically targets the kidneys and the lungs.

- Often, the first indication that patients have the autoantibody is when they cough up blood. But lung damage in Goodpasture's Syndrome is usually superficial compared with progressive and permanent damage to the kidneys.

- Goodpasture's Syndrome is a rare condition that affects mostly young men but also occurs in women, children, and older adults.

- Treatments include immunosuppressive drugs and a blood-cleaning therapy called plasmapheresis that removes the autoantibodies.

Reference: https://www.niddk.nih.gov/health-information/kidney-disease/glomerular-diseases

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2. SLE (Lupus) - There are two types of lupus. *Systemic lupus erythematosus (SLE)* is the form of lupus that can harm your skin, joints, kidneys and brain and may be fatal.

- The other form of lupus is called "*discoid" lupus erythematosus,* which affects only your skin. Systemic lupus erythematosus (SLE) that affects the kidneys is called *lupus nephritis.*

- Lupus nephritis causes inflammation (swelling or scarring) of the small blood vessels in the kidney (glomeruli) and sometimes the kidneys, by attacking them like they would attack a disease.

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Lupus nephritis can cause many signs and symptoms and may be different for everyone. Signs of lupus nephritis include:

- **Blood in the urine (hematuria):** Glomerular disease can cause your glomeruli to leak blood into your urine. Your urine may look pink or light brown from blood.
- **Protein in the urine (proteinuria):** Glomerular disease can cause your glomeruli to leak protein into your urine. Your urine may be foamy because of the protein.
- **Edema**: Having extra fluid that your kidneys cannot remove that causes swelling in body parts like your legs, ankles, or around your eyes.
- **Weight gain:** due to the fluid your body is not able to get rid of.
- **High blood pressure**

This condition is treated by a Nephrologist and Dietician, especially during periods of exacerbation.

Reference: https://www.kidney.org/atoz/content/lupus

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3. Autoimmune Vasculitis (i.e. ANCA Vasculitis) - In autoimmune vasculitis white blood cells attack one's own blood vessel walls causing swelling of the vessels.

- ANCA vasculitis is a type of autoimmune swelling caused by autoantibodies.
- ANCAs are autoantibodies that attack the cytoplasm of neutrophils. ANCA stands for Anti-Neutrophil Cytoplasmic Autoantibody.
- When ANCAs attack these neutrophils, they cause the white blood cells to attack the walls of small vessels in different tissues and organs of the body.
- In certain case the neutrophils respond by attacking the capillaries in the glomeruli of the kidneys, often causing an acute (and life-threatening) glomerulonephritis, with all the signs and symptoms of acute kidney failure. (edema ankles, weakness, anemia, nephrotic syndrome, hematuria, protein in urine, high creatinine, declining eGFR etc.)
- Treatment requires plasmaphoresis and dialysis, immuno-suppressive drugs, EPO injections, strict diet until condition is stabilized, phosphate binders etc.
- One in 50,000 people develop this condition (average age is 55 yrs)
- This condition is treated by Nephrologist and Dietician.

Reference: https://www.niddk.nih.gov/health-information/kidney-disease/glomerular-diseases

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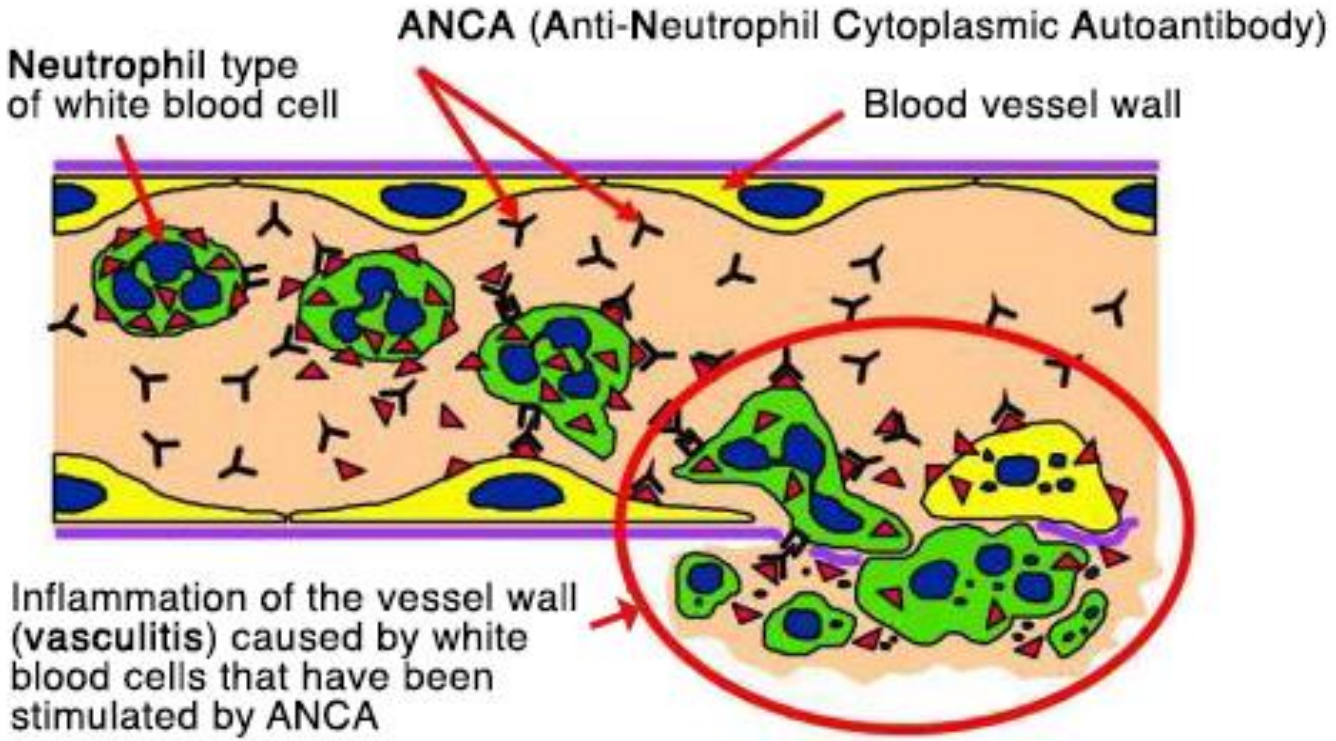
ANCA Vasculitis



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4. Wegener's Granulomatosis - Granulomatosis with polyangiitis is an uncommon disorder that causes inflammation of the blood vessels in your nose, sinuses, throat, lungs and **kidneys.**

Granulomatosis with polyangiitis, formerly called Wegener's granulomatosis, is one of a group of blood vessel disorders called vasculitis. It slows blood flow to some of your organs. The affected tissues may develop areas of inflammation called granulomas, which sometimes affect how these organs work.

- Early diagnosis and treatment of granulomatosis with polyangiitis may lead to a full recovery. Without treatment, granulomatosis with polyangiitis can be fatal.

Symptoms - Signs and symptoms of granulomatosis with polyangiitis may develop suddenly or over several months. The first warning signs usually involve areas of your respiratory tract, such as your sinuses, throat or lungs. The condition of people with this disease often worsens rapidly, affecting blood vessels and the organs they supply, such as the kidneys.

Signs and symptoms may include:

- Runny nose, stuffiness, sinus infections and nosebleeds
- Coughing, sometimes with bloody phlegm
- Shortness of breath or wheezing
- Fever
- Fatigue and general aches and pains
- Numbness in limbs, fingers or toes
- Weight loss
- **Blood in urine (hematuria)**
- Skin sores or bruising
- Eye redness, burning or pain
- Ear infections
- For some people, the disease affects only the lungs. When the kidneys are affected, you may not notice any early warning signs. But blood and urine tests can detect the problem. Without treatment, kidney failure and anemia often occur.

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Causes – largely unknown, but It appears to develop after an infection or other inflammation-causing event triggers an abnormal reaction from immune system. This reaction can lead to inflamed, constricted blood vessels and harmful inflammatory tissue masses (granulomas).

Age of Onset

- Granulomatosis with polyangiitis can occur at any age. It most often affects people between the ages of 40 and 65.

Complications

Besides affecting the nose, throat and lungs, granulomatosis with polyangiitis may affect skin, eyes, ears, kidneys, heart and other organs. Complications may include:

- Hearing loss
- Skin scarring
- Heart disease
- Kidney damage
- A loss of height in the bridge of the nose (saddling) caused by weakened cartilage
- Deep vein thrombosis

In cases of kidney involvement requires treatment by Nephrologist and Dietician

Reference: https://www.niddk.nih.gov/health-information/kidney-disease/glomerular-diseases

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5. **IgA nephropathy** is a form of glomerular disease that results when immunoglobulin A (IgA) forms deposits in the glomeruli, where it creates inflammation.

- The most common symptom of IgA nephropathy is **blood in the urine**, but it is often a silent disease that may go undetected for many years.

- The silent nature of the disease makes it difficult to determine how many people are in the early stages of IgA nephropathy, when specific medical tests are the only way to detect it.

- **This disease is estimated to be the most common cause of primary glomerulonephritis**—that is, glomerular disease not caused by a systemic disease like lupus or diabetes mellitus.

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- It appears to affect men more than women.

- Although IgA nephropathy is found in all age groups, young people rarely display signs of kidney failure because the disease usually takes several years to progress to the stage where it causes detectable complications.

- No treatment is recommended for early or mild cases of IgA nephropathy when the patient has normal blood pressure and less than 1 gram of protein in a 24-hour urine output.

- When proteinuria exceeds 1 gram/day, treatment is aimed at protecting kidney function by reducing proteinuria and controlling blood pressure.

- Blood pressure medicines—angiotensin—converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs)—that block a hormone called angiotensin are most effective at achieving those two goals simultaneously.

Reference: https://www.niddk.nih.gov/health-information/kidney-disease/glomerular-diseases

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Infection-related Glomerular Disease - Glomerular disease sometimes develops rapidly after an infection in other parts of the body.

1. Acute post-streptococcal glomerulonephritis (PSGN) can occur after an episode of strep throat or, in rare cases, impetigo (a skin infection). The *Streptococcus* bacteria do not attack the kidney directly, but an infection may stimulate the immune system to overproduce antibodies, which are circulated in the blood and finally deposited in the glomeruli, causing damage.

- PSGN can bring on sudden symptoms of swelling (edema), reduced urine output (oliguria), and blood in the urine (hematuria).

- Tests will show large amounts of protein in the urine and elevated levels of creatinine and urea nitrogen in the blood, thus indicating reduced kidney function.

- High blood pressure frequently accompanies reduced kidney function in this disease.

- PSGN is most common in children between the ages of 3 and 7, although it can strike at any age, and it most often affects boys. It lasts only a brief time and usually allows the kidneys to recover. In a few cases, however, kidney damage may be permanent, requiring dialysis or transplantation to replace renal function.

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2. **Bacterial endocarditis,** infection of the tissues inside the heart, is also associated with subsequent glomerular disease.

- Researchers are not sure whether the renal lesions that form after a heart infection are caused entirely by the immune response or whether some other disease mechanism contributes to kidney damage.

- Treating the heart infection is the most effective way of minimizing kidney damage.

- Endocarditis sometimes produces chronic kidney disease (CKD).

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3. HIV, the virus that leads to AIDS, can also cause glomerular disease.

- Between 5 and 10 % of people with HIV experience kidney failure, even before developing full-blown AIDS.

- HIV-associated nephropathy usually begins with **heavy proteinuria** and progresses rapidly (within a year of detection) to total kidney failure.

- Researchers are looking for therapies that can slow down or reverse this rapid deterioration of renal function, but some possible solutions involving immunosuppression are risky because of the patients' already compromised immune system.

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Final Considerations

Chronic Kidney Disease

- Most forms of glomerular disease develop gradually, often causing no symptoms for many years.
- CKD is the slow, gradual loss of kidney function.
- Some forms of CKD can be controlled or slowed down. For example, diabetic nephropathy can be delayed by tightly controlling blood glucose levels and using ACE inhibitors and ARBs to reduce proteinuria and control blood pressure.
- But CKD cannot be cured. Partial loss of renal function means that some portion of the patient's nephrons have been scarred, and scarred nephrons cannot be repaired.
- In many cases, CKD leads to total kidney failure.

Reference: https://www.niddk.nih.gov/health-information/kidney-disease/glomerular-diseases

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Nutritional Medicine In Kidney Disease:

- NM can be applied to help **slow CKD** in many cases – including novel dietary approaches outlined in these course notes and the careful, staged-in use of supplements.

- Be sure you know the cause (diagnosis) and stage of kidney disease before making any diet or supplementation recommendations. Be extra cautious in patients who received a kidney transplant and are on immuno-suppressive drugs.

- When introducing supplements monitoring of kidney function tests and urinalysis is imperative to make sure supplements are helping and not worsening kidney function.

- In remission states of autoimmune disease and recovery from drug-induced nephropathy states, diet and prudent supplements may also be helpful. Careful monitoring of kidney function is also mandatory to ensure supplement load is not inducing a strain on kidney function.

- During acute kidney disease from any cause, or in more advanced cases of kidney disease and failure, supplements may do more harm than good. I might consider only CoQ10 and supplements to increase Glutathione only in end-stage CKD, provided monitoring is undertaken.