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Role of Chronic Kidney Disease: A Literature Review

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Abstract: *- Chronic kidney disease is a broad term that includes subtle decrease in kidney function that develops over a minimum of three months. In contrast, acute kidney injury refers to any decrease in kidney function that happens in less than three months. now the kidney's job is to regulate what's in the blood, so we might remove waste, or make sure electrolyte levels are steady, or regulate the overall amount of water, and even make hormones- the kidneys do a lot of stuff.*

Keywords: *Chronic kidney disease; hypertension; diabetes; osteodystrophy; nephrons; Glomerular filtration rate*

Introduction:

Blood gets into the kidney through the renal artery, and once inside it goes gets into tiny clumps of arterioles called glomeruli where it's initially filtered, and the filtrate which is the stuff that gets filtered out, moves into the renal tubule. (Figure 1) The rate at which this filtration takes place is known as glomerular filtration rate or GFR. In a normal healthy person, this is somewhere around 100-120 milliliter of fluid filtered per minute per 1.73 meter square (100-120ml/min/1.73m²) to body surface area.(1) The value is slightly less in women than men and it decreases slowly in all of us as we grow older. One of the most common causes of chronic kidney disease is hypertension.(2) In hypertension, the walls of arteries supplying the kidneys begin to thicken in order to withstand the pressure, and that results in a narrow lumen (figure 2). A narrow lumen means less blood and less oxygen gets delivered to the kidney, resulting in ischemic injury to the nephron's glomerulus. Immune cells like macrophages and fat laden macrophages called foam cells slip into damage glomerulus and start secreting growth factors like transforming growth factor beta 1 or tgf-beta 1.(3) These growth factors cause the mesangial cells to regress back to their more immature stem-cell state known as mesangioblasts and secrete extracellular structural matrix. This excessive extracellular matrix leads to glomerularsclerosis, which is hardening and scarring which diminishes the nephrons ability to filter the blood and overtime this leads to chronic Kidney disease. The most common cause of chronic kidney disease is diabetes also, in the situation excess glucose in the blood starts sticking to protein in the blood a process called non enzymatic glycation because no enzymes are involved. This process of glycation particularly affects the efferent arteriole and causes it to get stiff and more narrow a process called hyaline arteriosclerosis. This creates an obstruction that makes it difficult for blood to leave the glomerulus, and increases pressure within the glomerulus which leads to hyperfiltration. Essentially pushing more fluid through it responds this high-pressure State, the supportive mesangial cells secrate more and more structural matrix which expanding the size of the glomerulus. Over many years, this process of glomerular sclerosis once again, diminishes the nephron's ability to filter the blood and can lead to chronic kidney disease. Although diabetes and hypertension are responsible for the vast majority of chronic kidney disease cases, there other causes as well including systemic diseases like lupus and rheumatoid arthritis, can

also cause glomerulo sclerosis. Other causes of chronic kidney disease include infections like HIV (4), as well as long term use of medications like NSAIDs and toxins like the ones in tobacco. Now, normally urea in the body gets excreted in the urine, but when there's decreased glomerular filtration rate, less urea gets filtered out, and therefore it has nowhere else to go besides the blood and so buildup in the blood which is a condition called azotemia, which can cause general symptoms like nausea and loss of appetite. As the urea levels really build up, they can affect the functioning of the central nervous system causing encephalopathy. This results in asterixis, a tremor of the hand that kind of resembles a bird flapping its wings and is best seen when the person attempts to extend their wrist. Further accumulation of these toxins in the brain can even progress to coma and death. This buildup can also cause pericarditis which is an inflammation of the lining of the heart. In addition, there can also be increased tendency for bleeding, since excess urea in the blood makes platelets less likely to stick to each other and so there's less clot formation. Finally, in some cases, someone can develop uremic Frost, where urea crystals can deposit in the skin and they look like powdery snowflakes.

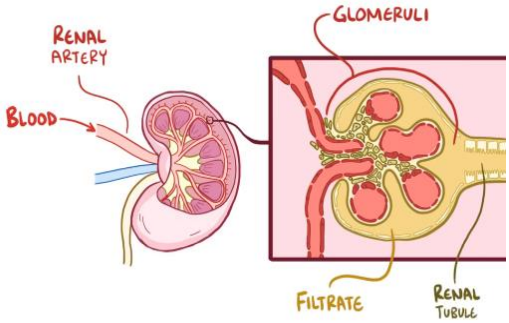

Figure 1 - kidney and its function

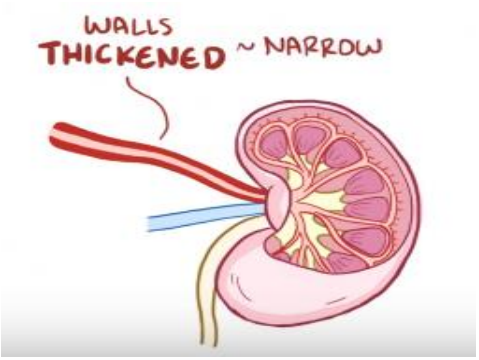

Figure 2 - Kidney with thickened wall in hypertension

In addition to getting rid of waste, the kidneys play important role in electrolyte balance. Potassium levels are particularly important, and normally the kidney helps with potassium excretion. In chronic kidney disease, though just like with urea, less potassium is excreted and some more builds up in the blood, and it leads to hyperkalemia, which can be problematic because it can cause cardiac arrhythmias(5). Another key role the kidneys relates to balancing calcium levels. Normally the kidney helps to activate vitamin D which helps to increase absorption of calcium from the diet. In chronic kidney disease, though there's less activated vitamin D, so less calcium is absorbed into the blood, which results in hypocalcemia- low calcium levels. As calcium levels in the blood fall, parathyroid hormone is released which causes the bones to lose calcium. Overtime this resorption of calcium from the bones leaves them weak and brittle, a condition known as renal osteodystrophy. The kidneys also release key hormones. For example, normally when the kidneys start sensing a lower than normal amount of fluid getting filtered, they respond by releasing the hormone renin to increase the blood pressure. In chronic kidney disease, the falling glomerular filtration rate leads to more and more renin secretion which leads to hypertension (6) (7). Now, remember that hypertension is a cause of chronic kidney disease itself, so this creates quite a vicious cycle. Finally the kidney also secretes the hormone erythropoietin which stimulates the production of red blood cells from the bone marrow. In chronic kidney disease, erythropoietin levels fall and this leads to lower production of red blood cells and ultimately anemia. (8)

Discussion:

It affects 11% of US population or about 30 million people, another 30 million people are at risk for developing ckd at some point in their lives. Early detection can help prevent the progression of ckd. Chronic kidney failure you can also be referred to as chronic kidney disease but failure I guess is the end stage and chronic kidney failure is essentially where you have loss an irreversible loss of the nephrons. The nephron is the functional units of kidneys. Anatomy slightly (figure 3) so the kidneys connects the ureter to the bladder. Bladder stores

urine ready for micturition. And here we have the inferior vana cava and the descending aorta which has vessels coming in and out from the kidneys. So there are many causes of chronic kidney failure and these include acute kidney injury or acute kidney failure, hypertension, diabetes and other kidney diseases. Other kidney diseases include polycystic kidney disease (9). So, all of this can lead to an irreversible loss of nephron. So let us look at each of these causes of chronic kidney. Acute kidney failure can lead to chronic kidney failure .acute kidney failure unlike chronic kidney failure is reversible and there are many causes of acute renal failure in itself. One way to categorize it is into prerenal causes, intrarenal causes and postrenal causes. So prerenal causes includes renal artery stenosis, heart failure and hemorrhage all which leads to acute kidney failure and then have intrarenal causes such as glomerular nephritis, tubular necrosis and interstitial nephritis, all this can also lead to acute kidney failure then have post renal causes such as an benign prostatic hyperplasia, renal stones and tumors. It is also important to note that prerenal causes and postrenal causes often lead to intrarenal causes essentially and this will all lead to acute kidney failure or acute renal failure.

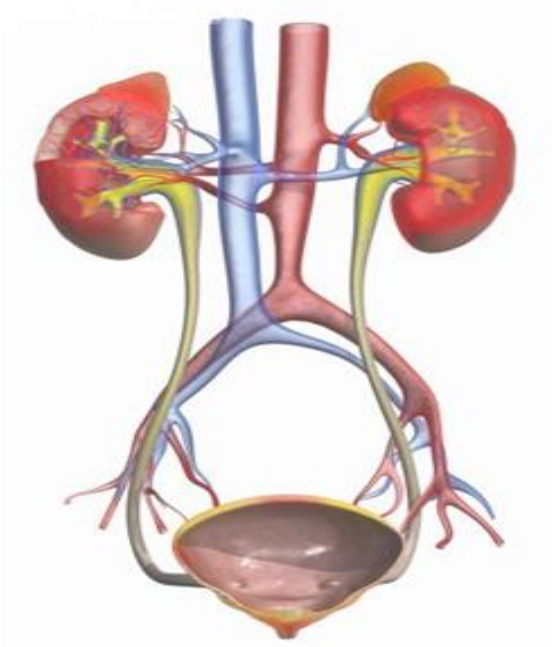

Figure 3: - kidney, ureter, bladder, inferior vana cava, abdominal aorta

Hypertension and how this can cause chronic kidney failure this kidney (figure 1) here which has a renal artery and renal vein leaving the kidney. The head of the nephron is the Bowman's capsule and it has capillaries entering and exiting. This is where blood you know is getting filtered through to the nephron. Now when there's normal blood pressure everything is smooth and everything is filtered. Head of the nephron and the Bowman's capsule area so blood vessels will enter this area these blood vessels originate. you know from the renal artery which enters the kidney when someone has hypertension it causes thickening of the blood vessels which leads to narrowing of the lumen because we have narrowing of the lumen there is less blood flow to the kidneys to the nephrons the afferent arteriole is a blood vessel which brings blood towards the head of the nephron but with less blood flowing through due to hypertension there is a decrease filtration (figure 2). So the point is when you have a decrease in blood flow to the nephron there are cells in this area that detect this and then start producing renin. This subsequently leads to the activation of the renin-angiotensin-aldosterone system (6). Now the renin-angiotensin-aldosterone system is a system which leads to increase in heart rate and further hypertension. This is unfortunate because less blood is flowing to the kidneys. Kidney thinks by increasing blood pressure it will receive more blood .it might work for some time but eventually the cycle will continue there is further vessel thickening and vessel narrowing. (6)(7) So it's a vicious cycle now this all eventually will lead to glomerulosclerosis which is thickening and hardening of the vessels in the Bowman's capsule in the glomerulus itself. Glomerular sclerosis inevitably leads to ischemic injury and so loss of the nephron itself. Most common cause of CKD is diabetes.(10) A massive complication in diabetes is diabetic nephropathy. Now diabetic nephropathy eventually will lead to CKD (11). As we know the Bowman's capsule and glomerulus these changes occur. The four main changes we see in diabetic nephropathy are (I) mesangial expansion and mesangial cell proliferation (II) podocytopathy which include podocytopathy hypertrophy and eventually atrophy (III) glomerular basement membrane thickening and (IV) sclerosis.(10) Sclerosis is essentially what we see in hypertension as well. So how do all these changes occur well

people develop diabetes because of risk factors include hypertension. Diabetes is condition High blood glucose leads to overproduction of reactive oxygen species now these reactive oxygen species .summary I'm just will lead to activation and production of unnecessary growth factors pro-inflammatory cytokines and producing essentially oxidative stress. All this leads to the four diabetic nephropathy changes. So going back to where we initially started a chronic kidney failure again is where you have irreversible loss of nephrons and this can be caused as we have learned by acute renal failure or acute kidney failure. Such as Hypertension, diabetes and other kidney diseases are polycystic kidney disease (9).

So, when you have loss of nephrons in the area. The blood flow will shift to nephrons that are still alive and working this leads to a glomerular hyperfiltration. for example a dead nephron essentially loss of nephron and functional nephron the blood flow will shift to the functional nephron leading to glomerular hyperfiltration there will be more blood flow. Now during the early stages glomerular hyperfiltration is tolerated we get to a big increase in GFR in the functional nephron after a while this hyperfiltration results in sclerosis because there's so much pressure and eventually glomerulus sclerosis will eventually lead to loss of that nephron as well and the cycle will continue. In the late stage you lose so much of your kidneys function that GFR decreases, urine output decreases and begin to retain waste resulting in uremia all this leads to the clinical manifestations of chronic kidney failure.

Clinical presentation or clinical manifestation:

(A) Sodium and water balanced: a decrease in GFR leads to increase in sodium and water retention which leads to an increase in blood pressure and peripheral edema(2). It is important to restrict fluid intake for these patients and when vomiting and diarrhea occurs in patients with chronic kidney failure this is very dangerous because of the already restrictive food intake further loss from vomiting and diarrhea can be very dangerous. (B) Potassium balance: a decrease in GFR leads to an increase in potassium retention this causes hyperkalemia which can result in muscle weakness it can result of ECG changes and cause fibrillation (5). It is important to note that the loss of nephrons leads to a decrease in renin production as well eventually which leads to a decrease in aldosterone. When you have a decrease in aldosterone the distal sodium potassium pump does not work which leads to potassium retention therefore using potassium sparing diuretics and ACE inhibitors can further aggravate a problem because you are essentially you're promoting more potassium and remember if in the nephron the sodium potassium pump the sodium potassium ATPase is at the distal part of the nephron and is responsible for the exchange between sodium and potassium so if aldosterone is not being produced this transported does not work and so we are retaining potassium. (C) Metabolic acidosis: we get diminished capacity you know in chronic kidney failure to excrete hydrogen and to generate bicarbonate which leads to the acidosis.(12) Acidosis can lead to Bone decalcification amongst many other things. So normally the nephron is responsible for maintaining the pH of our body the blood by producing bicarbonate if necessary or to secrete hydrogen ions if necessary.(13) (D) Mineral balance and osteodystrophy: now when you have loss of nephrons the kidneys cannot produce the hormone in normally produces which is a calcitriol now with no calcitriol. You have a decrease in calcium reabsorption from the GIT and the kidneys and this will lead to hypocalcemia(14). Hypocalcemia and a decrease in calcitriol will stimulate the parathyroid glands always continuously and this will lead to secondary hyperparathyroidism. Hyperparathyroidism State leads to osteodystrophy because of the hormone parathyroid hormone which actually stimulation bone breakdown and essentially. The loss of nephrons eventually also leads to a decrease in GFR and so you know when you have a decrease in GFR volume, decrease infiltration and so this will lead to hyperphosphatemia because the body cannot secrete phosphate.(15) (E) other manifestations of uremia: uremia is essentially a lot of urea in the blood. Urea is normally excreted by the kidneys in urine. So what normally happen to urea, the vasa recta are the blood vessels responsible for secretion of

substances into the nephron and the reabsorption of substances from the nephron. In the last part of the nephron the urea is actually reabsorbed into the vasa recta. Which helps drag water into these vessels urea then gets secreted back into the nephron because we don't want to keep it and the water just remains in the vessels because here the sodium is also reabsorbed allowing for equilibrium and so if this whole process does not work if the kidneys don't work at all you actually retain urea and so you would you get uremia and uremia is bad because it results in neurological signs and symptoms such as hiccups, cramps, gastro problems and erection , vomiting, reproductive changes including decrease in estrogen and testosterone resulting and amenorrhea and impotence and this uremia also result in some skin changes .

Diagnosis:

Blood: normocytic normochromic anaemia, Increased ESR, Increased urea level, Increased serum creatinine, Decreased calcium, Increased phosphate level, Increased Alk. Phosphatase, Increased parathyroid hormone level.

Urine: urine routine examination for 24 HRs protein and creatinine clearance.

Radiology: Renal USG: exclude obstruction, renal size assesment, usually kidney size is decreased, but may not decrease in case of DM, PKD, amylodosis myeloma.

Chest radiograph: cardiomegaly, pleural effusion, pericardial effusion or signs of pulmonary oedema.

Bone radiographs for renal osteodystrophy.

Chronic kidney disease comes down to looking at changes in the glomerular filtration rate over time. Chronic kidney disease might be suspected with a GFR of less than 90 ml per minute per 1.73 m squared (1). Irreversible kidney damage might happen with the GFR below 60 ml per minute per 1.73 m squared. (1) To confirm, the diagnosis of kidney biopsy can be done to look for changes like glomerulosclerosis.(16)

Treatment:

Control the water inflow, low protein diet (0.6-0.8mg/kg body weight per day): add essential amino acid, Decrease sodium (1-4gm), Decrease potassium, Decrease phosphorous (<1000mg/day), Erythropoetin and Vit-D supplement, symptomatic treatment, Renal replacement therapy-Peritoneal dialysis, Hemodialysis, Renal transplantation.

I. Treat reversible causes-Relieve obstruction, Stop nephrotoxic drugs,Treat hypercalcemia
II. Emergency management-Treat hyperkalemia ,Treat for acidosis, Heart failure
III. Treat the complications- Manage pulmonary edema promptly, Manage hyperkalemia (can be life threatening)(5).
IV. Treat hypertension: A small decrease in BP increases significant renal function. ACEI & ARB decrease the rate of loss of function even if BP is normal. AIM FOR BP <130/80 AND <125/75 IF >1gm proteinuria per day.
V. Treat oedema: High dose loop diuretics and restriction of fluid intake.
VI. Osteodystrophy: Restrict dietary po4. Prescribe phosphate binders (Calcium Carbonate) and VIT- D analogues.
VII. Diet: Match dietary intake of fluid acc. to the excretion. Sodium restriction may be useful, moderate protein diet, Restrict dietary potassium in case of hyperkalemia. Chronic kidney disease often involves managing the underlying cause. In severe situations, dialysis or kidney transplant might be needed. It is important to realize that dialysis is just a tip of the iceberg. chronic kidney disease is a prevalent yet silent disease most patients do not know that they have it since ckd is not associated with clear symptoms till the disease is quite advanced therefore it is important to screen patients at increased risk developing chronic kidney disease.(17)

Conclusion:

Chronic kidney disease is when the glomerular filtration rate falls below 90 ml per minute per 1.73 m squared over at least three months. Chronic kidney disease is mainly caused by diabetes and hypertension and complications include electrolyte abnormalities, accumulation of toxin buildup,

hypertension and weak bones. So that was most of the clinical manifestations in chronic kidney failure. finally as we have mentioned briefly chronic kidney disease when a lot of nephrons are lost this will eventually result in a decrease in renin production resulting in a decrease in blood pressure and decrease in erythropoietin which result in anemia (8) and also as I mentioned earlier a decrease in the production of the hormone calcitriol which causes renal osteodystrophy.

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Conflicts of interest:

The authors declare no conflicts of interest.

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