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Urinary Biomarker Alterations Associated with Chronic Kidney Dysfunction

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ABSTRACT: This study examines the complex physiology of furine, its production, and its crucial connection to chronic kidney disease (CKD). Three essential mechanisms—glomerular filtration, future perceptive tubular reabsorption, and tubular secretion—are involved in kidney creation, chronic kidney disease, and urine generation. These activities cooperate to preserve homeostasis by controlling fluid balance and waste removal

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INTRODUCTION: The kidneys play a crucialrole in maintaining homeostasis by regulating fluid balance, electrolyte levels, and waste elimination through urine formation. This complex process involves three key steps: glomerular filtration, tubular reabsorption, and tubular secretion. These mechanisms work together to ensure the body's internal environment remains stable, which is essentialforoverallhealthandwell-being.Chronic kidney disease (CKD) is a progressive condition marked by the gradual loss of kidney function,often caused by underlying factors such as diabetes and hypertension. Over time, repeated damage to thenephronsdiminishesthekidneys'abilitytofilter blood effectively and produce urine.

Thisdeclineinkidneyfunctioncanresultinserious complications, including fluid overload, electrolyte imbalances, and an increased risk of cardiovascular disease. Understanding the physiology of urine formation is vital for comprehending the pathophysiological changes that occur in CKD. Such knowledge provides insight into howimpaired kidney function disrupts homeostasis and contributes to the progression of the disease.

Early detection of CKD is critical, as timely interventionscanhelppreservekidneyfunctionand prevent or delay complications. This reviewfocuses on the intricate connection between the processesofurineformationandCKDprogression.

It highlights the importance of identifying CKD in its early stages and implementing effective management strategies to improve patient outcomes.Byadvancingourunderstandingofthese relationships, we can develop better approaches to mitigating the impact of CKD and enhancing the quality of life for affected individuals

[1-5].

Relevant Physiology of Urine Formation: The formation of urine begins with glomerular filtration (GF)inthecaseoffornication.Asarule,about180 liters of fluid are filtered every day. All soluble blood components are removed by plasma proteins (and related substances) and lipids are filtered by the beads. More than 99% of the glomerular filtrate isreabsorbedbytherenaltubules.Approximately 1.5litersof urineisproduced in24 hours.

Diuretics act primarily by inhibiting renal tubular reabsorption. A 1% decrease in tubularreabsorption can more than double urine volume. The mechanisms that move ions across tubularcells are complex and involve multiple energy- dependent transmembrane pumps as well as channels between closely adjacent proximal tubule (PT) cells. All Na +falling into the urinary tube cells via the cleaning membrane is pumped up in the intelligence of the kidney on the basement membrane using at Atpase. Since K +has a large cage with an extracellular gradient, the antiport of NA +-K +conditions increase the K +canal. For simplicity, tubular recovery can be divided intofour regions [6].

Site I: Proximal tubule four mechanisms of Na+ transport have been defined in this segment (a) Direct entry of Na+via favourable electrochemical gradient.Itisanelectrogene.(b)Active- coupledNa+ and K+transport reabsorption of glucose, amino acids, other organic anions and $PO4^{3-}$using specialsymporters. There is only glucose-coupledNa+ reabsorption electrogene. (c) Exchange with H+: Pt -TiesreleasesH+ from Na+- H+ anti -porters (Exchange Na+-h+) in the light film. This replacement moves Na+ from urinary tipon to internal cells. The released H+ combines with HCO3. Carbon dioxide is formed in thetubular fluid. This H2CO3 is split into H2O + CO2 attached to the brush border, as it is very slowly decomposed in part by H2CO3 (type IV enzyme). Practically all $HCO3^{-}$ is reabsorbed in PT by this mechanism, because tubular membrane, as such, is relatively impermeable to HCO3-. (d) Disproportionately large reabsorption of $HCO3^{-}$ acetate, $PO4\ 3^{-}$, amino acids, and other anions creates passive driving forces for Cl^{-} diffusion through the paracellular pathway (between tubular cells), especially in late PT. This takes up Na+ and watertomaintainelectricalneutralityand isotonicity; reabsorption in the PT is isotonic. A major part of filtered K+ is reabsorbed in the PT. Thus, an isotonic tubular fluid with major changes in composition enters the thin descending limb of loop of Henle.

Section II: Ascending Loop of Henle (Asc LH). The thick part of the Asc LH can be divided into two distinct parts: (i) the medulla, lined with cuboidal cells. (ii) the cortex, lined with flattened cells. Both parts are relatively impermeable towater but actively absorb salt, diluting the tubular fluid. In the brain, another luminal membrane transporter transports ions in the stoichiometric ratio Na+-K+-2Clâ and is not electrogenic. Na+thatentersthecellispumpedintothee.c.f.Na+K+ ATPase on the basolateral membrane. In addition, the Na+-Cl^{-} symporter moves Cl^{-} down its electrochemical gradient into the e.c.f. and transports Na+. As the tubular fluid passes through the AscLH, it becomes progressively hypotonic. AccumulationofNaClinthemedullaryinterstitium without water makes the medullary interstitium hypertonic and establishes a corticomedullary osmotic gradient: it draws water from the descending limb of the loop of Henle (this thin segment is highly permeable to water but has no active transport of NaCl), so that the fluid entering the AscLH becomes hypertonic.

Site III: Diluting cortical segment of the loop of Henle this segment, also impermeable to water, continues to absorb salt, but here it is via a Na+- Cl^{-} symporter. The luminal fluid becomes further diluted. Site III: Cortical diluting segment of loop of Henle this segment, also impermeable to water, continues to absorb salt, but here it is through a Na+-Cl^{-} symporter. Tubular fluid gets further diluted.

Site IV: Distal tubule (DT) and collecting duct (CD) in the late DT and late CD, Na+ is again actively reabsorbed. Cation and anion balance is maintained partly by passive diffusion of Cl- and partly by secretion of K+ and H+. Na+ uptake at thissiteoccursviaspecificamiloride-sensitiveNa+ channels and is largely controlled by aldosterone (seediagram).Thisallows youtopreciselyregulate your electrolyte production according to your body's needs. Like other cells, DT and CD cells are

richinK+;thereisachemicalgradientforits diffusion into the tubule lumen, facilitated by the negative transepithelial potential difference of the lumen in this part of the tubule. The luminal membrane has an active secretory pump for H+ which is in turn regulated bythe movement of Na+ in the opposite direction. Diuretics acting near aldosterone-sensitive ion exchange sites increase the supply of Na + to the distal nephron and increase its exchange for K+, which is therefore reabsorbed into the PT and AscLH and secretedintotheDTandCD.ThenetlossofK+isregulated by changes in secretory processes and depends on:

1. TheNa+load deliveredto distal segment
2. Presenceorabsenceof aldosterone
3. (AvailabilityofH+
4. IntracellularK+stores

Free Water Clearance: Free water clearancerefers to the amount of urine excreted per unit time that exceeds the volume needed to excrete solutesin isotonic equilibrium with plasma. This value is positive when dilute urine is produced in the absence of antidiuretic hormone (ADH) and negative when concentrated urine is formed under the influence of ADH. When urine is isotonic, free water clearance is zero, regardless of the urine volume. The generation of both positive and negative free water clearance relies on the establishment of a cortico-medullary osmotic gradient, a process inhibited by diuretics acting on the medullary ascending limb of the loop of Henle (AscLH).In the proximal tubule (PT), organic ion transport operates through a nonspecific bidirectional active transport system for organic acids and bases. However, the extent of transport varies between substances. For instance, uric acidis typically reabsorbed to a greater extent than it is secreted, while the opposite is true for penicillin.

Several clinically significant diuretics, including furosemide, thiazides, and amiloride, utilize this transport mechanism to reach their sites of actionon the luminal side of the renal tubule, particularly in the AscLH, distal tubule (DT), and collecting duct (CD). These diuretics target specific processes toinfluenceurinecompositionandvolume,playing a vital role in the treatment of various renal and cardiovascular conditions. Chronic Kidney Drug: Chronic kidney disease (CKD) is a prevalent health condition, affecting an estimated 800 million individuals globally. AccordingtotheKidneyDisease ImprovingGlobal Outcomes (KDIGO) guidelines, the measurementor estimation of glomerular filtration rate (GFR) isa cornerstone in the diagnosis and management of CKD. GFR assessment provides critical insights into the severity and progression of the disease, enabling clinicians to implement timely interventions.

Early detection and effective management of CKD are essential to prevent its progression and reduce the risk of complications, including cardiovascular diseases and kidney failure.GFR measurement or estimation is widely regarded as an invaluable diagnostic tool for CKD. It helps determine the functional status of the kidneys and guides treatment decisions. In addition to GFR, biochemical markers and urinarybiomarkers playa significantroleinunderstandingCKDpathogenesis and progression. Albuminuria, a key biomarker, is both accessible and cost-effective, often detected through standardized urinalysis test strips. It serves as an early indicator of CKD and is strongly associated with an increased risk of cardiovascular events. The level of proteinuria is directly proportional to cardiovascular risk, emphasizingthe importance of regular monitoring in CKD patients.Chronic kidney damage can be diagnosed when abnormal kidney function persists for at least three months or when albuminuria is detected despite normal kidney function. Structural or morphological abnormalities, such as polycystic kidneydiseaseinadults,alsoindicateCKD.During the disease's progression, irreversible damage tothe glomeruli and tubules often occurs, which can be anticipated using advanced biochemicalmarkers.

Amiloride, a diuretic, utilizes the transport mechanism in the proximal tubule to reach its site of action on the luminal side of the renal tubule, particularly in the ascending limb of the loop of Henle (AscLH), distal

tubule (DT), and collecting duct (CD). This mechanism underscores the intricate interplay of transport systems in the kidneys and their relevance in both disease pathogenesis and treatment strategies. A comprehensiveunderstandingoftheseprocessesis

vital for developing effective diagnostic and therapeutic approaches in CKD management [7-12].

Chronic Medications for Renal Therapy: The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that measurement or estimation of glomerular filtration rate (GFR) is an important diagnostic tool for CKD [13]. Early diagnosis and treatment of CKD are essential to prevent disease progression and minimize the risk of side effects. Accurate assessment of SCF is important in this regard as it provides valuable information on the severity and progression of CKD. Measurement or assessment of SCF iswidely recognized as important in the diagnosisand treatment of CKD and is important in clinical guidelines [14].

A five-stage classification system based on GFR levels provides clinicians with a basis to assess the severity of CKD and adapt treatment strategies accordingly Table 1 many diseases and potentially toxicsubstancesareinvolvedinthedevelopmentof CKD. However, during the pathogenesis of CKD, irreversible damage to the glomeruli and tubules develops, which can be predicted using several biochemicalmarkers[15]. IntheearlystagesofCKD, albuminuria is the most readily available and standardized urinary biomarker, and the use ofurine dipstick tests is cost-effective.Albuminuria is apredictorofCKDand furtherincreases the risk of cardiovascular disease [14,16].

Cardiovascular risk also depends on the level of proteinuria. Chronic kidney disease may be diagnosed if renal failure persists for at least 3 months or if abnormal albuminuria is detected despite normal renal function. CKD can also manifest as structural or morphological abnormalities of the kidney(e.g., polycystic kidney disease in adults) [13]. The gradual decrease in the number of nephrons has been identified as a significant factor in the gradual narrowing of the glomerular filtration rate (GFR). As CKD progresses, the renal function gradually declines. Typical uremic symptoms are observed in patients with severely advanced and untreated kidney damage. Along with the gradual deterioration of kidney function, many accompanying clinical symptoms can be observed as a result of impaired physiological function of the kidneys. TABLE 1: STAGES OF CHRONIC KIDNEY DISEASE (CKD) BASED ON ESTIMATED GLOMERULAR FILTRATION RATE (EGFR)

CKD stages	Description	Egfr(ml/min/ 1.73m$^{2)}$
G1	Mildrenalimpairmentwith normalorreducedGFR	>90
G2	Kindlydamage,slightly reduced GFR	Between60-89
G3a	Mildlytomoderately reducedGFR	Between45-44
G3b	Moderatelytoseverely reducedGFR	Between30-44
G4	SeverelydecreasedGFR	Between15-29
G5	Renalfailure	<15(orrenal replacement

Delaying the Advancement of Chronic Kidney Disease: There are two crucial responsibilities involved in kidney support. prevention and slowing the progression of chronic kidney disease (CBP). Regardless of whether they have high blood pressure and diabetes, persons with high blood pressure are at a considerable risk of developing cardiovascular disease and dying from it. Furthermore, deaths from chronic kidney disease, particularly cardiovascular disease, are more likely to occur than those necessary to start renal replacement treatment 17, 18. Preventing renal disease and the advancement of chronic kidney disease is thus essential. Slowing the course of CKD requires addressing the underlying problems that cause it. For example, it is advised to treat hematological disorders, diabetes, hypertension, primary glomerular illnesses, and Autosomal Polycystic Kidney Disease (ADPKD). Rapidly managing reversible processes, including potential restriction of urine flow, is the easiest way to delay the course of renal disease.

A daily protein intake of 0.8 g/kg body weight has been shown in clinical trials to slow the course of CKD 20. In addition to lowering blood pressure, a low-salt diet will also lessen salt retention. It is advised that you consume no more than two to three grams of sodium per day from meals, or around five grams of table salt. You may considerably lower your risk of hypertension and associated cardiovascular illnesses by heeding these recommendations. 20–21. Treating metabolic acidosis with sodium bicarbonate treatment is not the same as cutting down on salt.
Sodium bicarbonate treatment has been shown in several published trials to have no discernible impact on systemic blood pressure. 23, 24.
Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) have been shown to lower the risk of cardiovascular events (CVEs) and postpone end-stage renal disease (ESRD) in patients with chronic kidney disease (CKD) [39–41]. Clinicians may decide to treat hypertension using ACEIs if there are no contraindications, while intolerance 27 is treated with ARBs. Multiple antihypertensive medications may be necessary for CKD patients, who often have resistant hypertension 28. Angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) have been recognized for their ability to decrease the course of chronic kidney disease (CKD), preserve kidney function, and reduce urine protein excretion. These medications lower intraglomerular pressure and decrease output.

of primary ultrafiltrate, reducing the tubular epithelium's reabsorption burden. This lowers the amount of fluid, electrolyte, and organic material that the tubules need to process. ACEIs are known to considerably increase cerebral blood flow, despite the fact that they do not directly change renal blood flow. According to Fig. 1, ACEIs and ARBs provide the greatest renal advantages in CKD patients who have proteinuria. They must be stopped as antihypertensives, nevertheless, since in certain circumstances, their usage may result in deteriorating renal function and higher blood potassium levels. It is crucial to evaluate the ongoing use of these medications in cases of serious renal damage. It's interesting to note that stopping ACEIs or ARBs in severe CKD often has no effect on renal function. Conversely, it could hasten the onset of renal failure and increase the risk of extracellular volume (ECV) enlargement. As a result, ACEIs and ARBs are still essential for treating chronic kidney disease (CKD), although patients with significant renal impairment need to be closely monitored and treated accordingly 29–32.

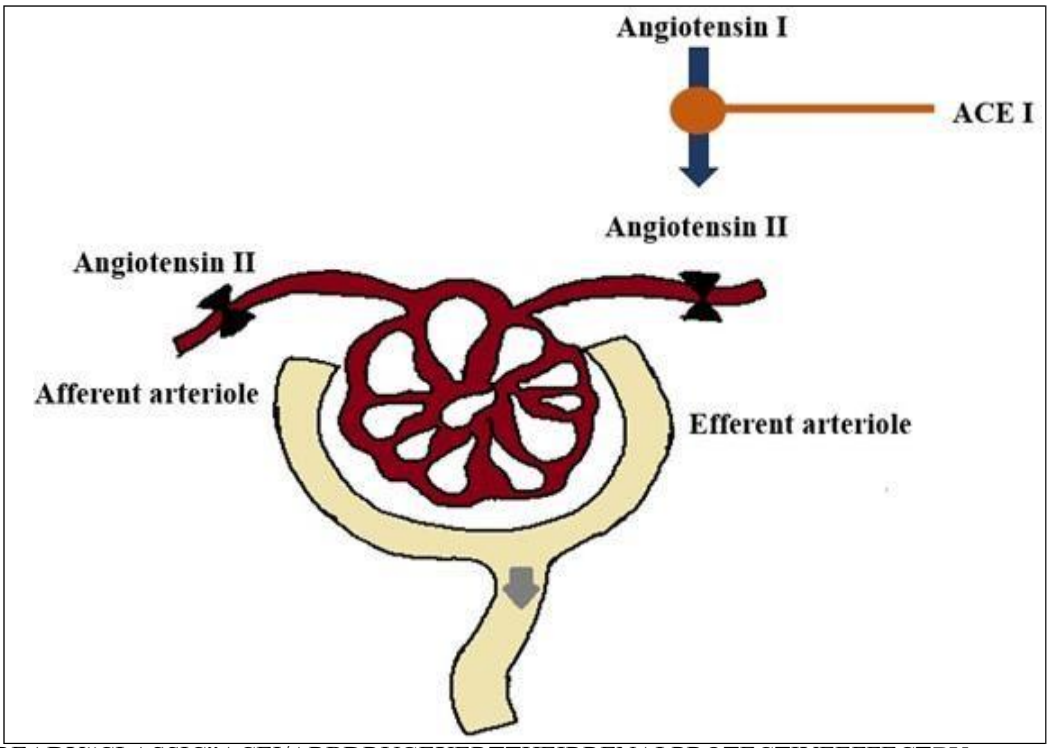
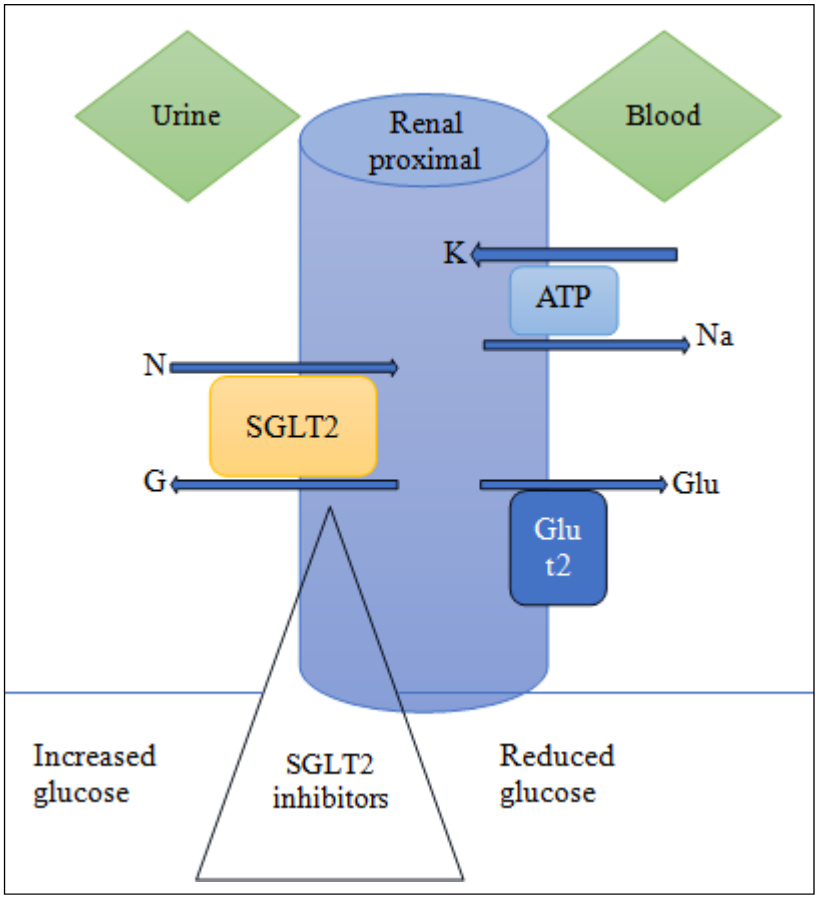


FIG.1:THEALREADY“CLASSIC”ACEI/ARBDRUGEXERTTHEIRRENALPROTECTIVEEFFECTBY

REDUCINGINTRAGLOMERULARPRESSURE.Abbreviation:Ace-1:AngiotensinConvertaseEnzymeInhibitors.

Steer clear of nonsteroidal anti-inflammatory medications: Because prostaglandins are necessary for sustaining renal blood flow, non-steroidal anti-inflammatory medicines (NSAIDs) affect kidney function by preventing their generation. This is brought on by the suppression of the cyclooxygenase enzymes COX-1 and COX-2, which results in decreased glomerular blood circulation and vasoconstriction in the renal blood vessels. Furthermore, NSAIDs may cause salt retention, which raises blood pressure and puts more strain on the kidneys. Long-term NSAID usage has serious dangers since it may eventually cause irreparable kidney damage, especially in elderly persons. These side effects highlight how crucial it is to use NSAIDs with caution. Except in situations when their advantages exceed the hazards, they should mostly be saved for treating acute medical issues rather than long-term usage. It is advised to reduce possible impairment to kidney function, particularly in susceptible groups, by using alternate therapy and proper monitoring. Utilizing Inhibitors of Sodium-Glucose Cotransporter-2 (SGLT2): Inhibitors of sodium-glucose cotransporter 2 (SGLT2) are vital medications that are often used to treat kidney illness and chronic kidney disease (CKD). Because they efficiently lower blood sugar levels, these medications were first approved by the U.S. Food and Drug Administration (FDA) in 2013 for the treatment of type 2 diabetes. They do this by preventing the proximal tubules of the kidneys from reabsorbing glucose, which increases the amount of glucose excreted via urine and aids in the management of hyperglycemia. Figure 2. In addition to its use in the treatment of diabetes, SGLT2 inhibitors have shown promise in the treatment of heart failure, demonstrating their adaptability and significance in the management of other chronic illnesses. These medications significantly protect the kidneys and heart in addition to lowering blood sugar. They have so emerged as a key component of treatment plans, providing a thorough method for improving the prognosis of patients with heart failure, CKD, and type 2 diabetes.



Inhibitors of SGLT2 include increased excretion of glucose and sodium. By halting other physiological processes, we may see the beneficial effects of such treatment, such as in heart failure or slowing down the progression of chronic kidney disease (CKD). Shorthand: Glut2: glucose transporter 2, SGLT2, sodium/glucose cotransporter 2, ATPase: adenosine 5-triphosphatase, Na, natrium, K, potassium. Additionally, SGLT2 inhibitors have a minor add-on diuretic effect by decreasing sodium reabsorption, which raises natriuresis 33. However, the tubuloglomerular feedback was normalized due to an increase in sodium input into the macula densa. Intraglomerular pressure decreases as a consequence of the afferent arteriolar vasoconstriction that follows 34–35.
Even in individuals with proteinuria and no diabetes, SGLT2 inhibitors have been shown to reduce the course of CKD 13, 19, 36, 37. Guidelines advise the use of SGLT2 inhibitors in CKD patients with acceptable RAAS inhibition based on 1B evidence 13.

Blockade of the Mineralocorticoid Receptor (MRA): The steroid hormone aldosterone is essential for controlling the action of mineralocorticoids. It is produced in the adrenal cortex's zona glomerulosa and mainly serves to encourage potassium excretion and sodium reabsorption in the renal system's cortical collecting duct. Blood pressure control, fluid and electrolyte balance, and general homeostasis all depend on this system. Recent studies have, however, shown the important role aldosterone plays in the onset of renal and cardiovascular disorders, with its overactivation leading to serious pathological alterations. Aldosterone has many harmful impacts on the cardiovascular system. It may make heart failure worse by encouraging meningeal inflammation, ventricular remodeling, and myocardial hypertrophy. Aldosterone also worsens the course of cardiovascular disease by decreasing coronary blood flow and causing myocardial ischemia. These negative consequences highlight how crucial it is to control aldosterone activity in people with heart disease. Aldosterone also has a negative impact on the kidneys. It is linked to increasing kidney damage, proteinuria, glomerular hypertrophy, and glomerulosclerosis. One important indicator of kidney damage and the advancement of chronic kidney disease (CKD) is proteinuria. Aldosterone is a key target in the treatment

of these conditions because of its cumulative effects on the cardiovascular and renal systems. Aldosterone antagonists are often used in conjunction with ACE inhibitors or angiotensin receptor blockers (ARBs) to reduce the course of chronic kidney disease. By lowering proteinuria, this combination medication has been shown to preserve renal function. Aldosterone antagonist usage, however, entails the risk of hyperkalemia, a disorder characterized by high blood potassium levels.
Because hyperkalemia may worsen renal and cardiovascular problems, it is especially dangerous for individuals with CKD or those on ACE inhibitors or ARBs. Non-anion gap metabolic acidosis (NAGMA), a minor type of metabolic acidosis, may also occur in patients who have modest hyperkalemia while on ACE inhibitor or ARB medication. Supplementing with sodium bicarbonate (NaHCO3) is often advised in these situations. In addition to correcting metabolic acidosis, this method improves and may even reverse hyperkalemia, bringing electrolyte balance back. Nonsteroidal mineralocorticoid receptor antagonists (MRAs) have become a safer and more selective substitute for aldosterone antagonists, notwithstanding the latter's effectiveness. With a far decreased chance of producing hyperkalemia, these medications significantly reduce proteinuria. Finerenone is one such nonsteroidal MRA that has shown encouraging outcomes in clinical trials. Finerenone efficiently lowers levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker linked to heart failure, and albuminuria, a sign of kidney injury.
Crucially, finerenone accomplishes these advantages without raising the risk of hyperkalemia, which makes it a safer choice for people with cardiovascular diseases and chronic kidney disease. Aldosterone's detrimental effects on the kidneys and heart emphasize the necessity for efficient treatment methods.
Clinicians may now more effectively control the dangers associated with aldosterone overactivation with to improvements in therapeutic options, such as the development of nonsteroidal MRAs like finerenone. These treatments provide a viable avenue for enhancing patient outcomes in the management of CKD and cardiovascular disease by treating proteinuria and reducing unfavorable side effects 39–41.

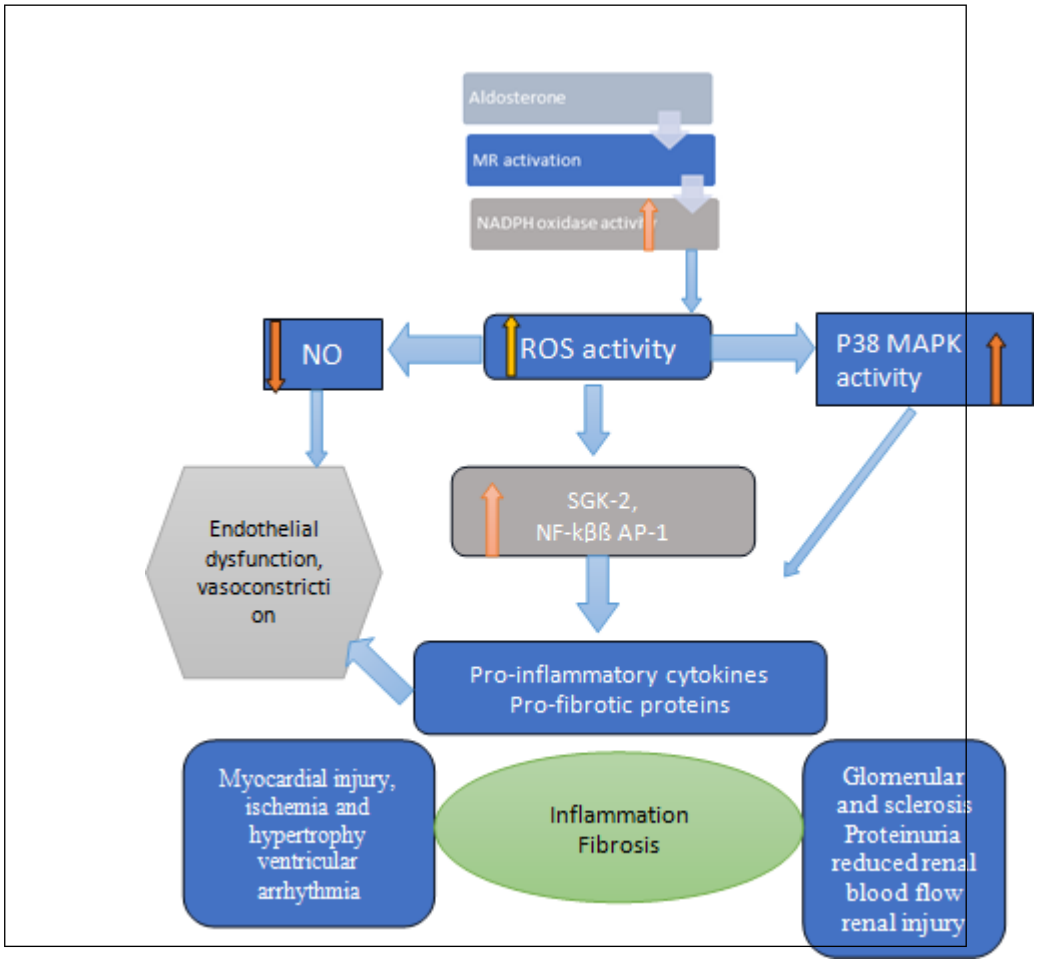


FIG. 3: THE CARDIOVASCULAR SYSTEM BOOSTS FROM THE AMELIORATION OF ALDOSTERONE ACTIVITY BY REDUCCING OR INHIBITING ITS FUNCTION. Furthermore, it is a useful tool for slowing the progression of chronic kidney disease (CKD). Shorthands: NADPH, nicotinamide adenine dinucleotide phosphate oxidase; AP-1, activator protein 1; MRA, mineralocorticoid receptor antagonist; NF-B, nuclear factor kappa-light-chain-enhancer of activated B cells; ROS, reactive oxygen species; Serine/threonine-protein kinase, or SGK-1
Renal anemia treatment: Early on in CKD (stage 3a), renal anemia may develop. Anemia causes tissue hypoxia, which accelerates the process. 42. Reducing anemia could enhance the medulla's ability to receive oxygen. Reduced erythropoietin production is the cause of renal anemia 43. After ruling out alternative reasons, including iron deficiency, a diagnosis may be established 44,45. if the patient has a hemoglobin concentration (HTC < 0.33%) that is continuously less than 11 g/dl. Treatment with erythropoietin should be started after secondary causes of anemia have been eliminated (13). Numerous drugs are available to promote the generation of red blood cells 46 in modern medical practice. These medications include human recombinant erythropoietin products. At present time, there are hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI) that may be used for this purpose. CKD-metabolic Bone disease: Holding on starts early in chronic kidney disease (CKD) and has a role in secondary hyperparathyroidism development. The activity of many hormones that control the levels of calcium and phosphate is essential for maintaining healthy mineral and bone metabolism. These include calcidiol or 25 (OH)D3, which is the precursor of calcitriol, calcitriol or 25 (Hyperphosphatemia is a frequent consequence of chronic kidney disease (CKD), and parathyroid hormone (PTH). FGF23/klotho, calcitonin, and phosphate OH)2D3 (the strongest type of the vitamin D hormone system). These hormones are important for preserving metabolism and bone health. Numerous bodily indicators, such as calcium, phosphate, PTH, FGF23/Klotho, and the vitamin D hormonal system, which includes calcidiol and calcitriol, may be markedly changed by chronic kidney disease (CKD). Reduced bone mass, more fragility fractures, and arterial and valvular calcification are just a few of the negative clinical consequences that may

result from these alterations in bone and vascular metabolism. 47. RESULTS: A vital physiological process, urine generation involves tube secretion, tubular reabsorption, and glomerular filtration, all of which preserve fluid and electrolyte balance and get rid of waste products from metabolism. Due to gradual nephron destruction, chronic kidney disease (CKD) interferes with these processes, resulting in a reduction in glomerular filtration rate (GFR) and the buildup of harmful compounds. The patient's quality of life is greatly impacted by the many problems that result from this illness, such as fluid overload, electrolyte imbalance, and hypertension.

Knowing the fundamentals of urine production physiology helps one better understand the processes behind chronic kidney disease (CKD) and emphasizes the significance of early identification and treatment approaches. To delay the course of the illness, interventions such medication treatment, lifestyle changes, and renal function monitoring are crucial. In the end, this information emphasizes the intricate connection between kidney function and general health and the need of ongoing research and clinical care to improve outcomes for patients with CKD.

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