EXPLORING CARDIO-RENAL SYNDROME: INTERACTIONS BETWEEN HEART AND KIDNEY HEALTH

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ABSTRACT

Chronic kidney disease (CKD) affects over 800 million individuals worldwide, significantly elevating the risk of cardiovascular disease (CVD). The interplay between heart and kidney functions leads to a condition known as Cardio-Renal Syndrome (CRS), wherein dysfunction in one organ can exacerbate illness in the other. Key clinical manifestations of CRS include increased venous and renal pressure, hemodynamic changes due to altered neurohormonal signals, and disruptions in the heart-kidney axis. Recent evidence highlights that venous congestion plays a crucial role in the progression of both heart and kidney disorders. This review explores the intricate relationship between the heart and kidneys, outlining CRS classifications, biomarkers, pathophysiology, and treatment strategies, emphasizing the need for integrated management approaches to improve outcomes for affected patients.

KEYWORDS

Cardio-renal syndrome, chronic kidney disease, cardiovascular disease, GFR, reno-cardiac syndrome, hypertension, diabetes mellitus and heart failure.

INTRODUCTION

Chronic kidney disease (CKD) has been defined and classified differently over time. However, up-to-date global standards define CKD as diminished kidney function indicated by a glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m2 or markers of kidney disease, or both, of a minimum of three months duration, irrespective of the root cause of the disease.[1] More than 800 million individuals globally suffer from chronic kidney disease (CKD), which is a serious public health problem that is predicted to rise in frequency due to rising rates of hypertension and diabetes mellitus. [2] Cardiovascular disease (CVD) is primarily responsible for the death and disability rates of individuals with chronic kidney disease (CKD), with a significantly higher probability of cardiac events in adults and children. The risk of cardiovascular death increases as CKD severity increases, eventually reaching 100 times the rate in people without the condition. There is a significant correlation between

elevated cardiovascular mortality and even mild-to-moderate renal function decline. [3] By regulating cardiac output, hydration status, and blood vessel tone in concert, the heart and kidneys preserve hemodynamic stability. Bidirectional disorders of heart and kidney function are caused by the interaction between these two organs, wherein one organ can cause or exacerbate illness in the other is defined as Cardio-renal syndrome (CRS). Regardless of their degree of left ventricular function, about 30% of patients with acute heart failure (AHF) had a lower GFR at baseline. [4]

CLASSIFICATION OF CARDIO-RENAL SYNDROME

CRS type 1- Acute cardio-renal syndrome: Acute cardio-renal syndrome, is marked by an abrupt deterioration in heart function that results in acute kidney damage. Acute cardiac diseases, such as acute decompensate heart failure, valvular disease, pulmonary embolism, and acute coronary syndrome. [5]

CRS type 2- Chronic cardio-renal syndrome: Chronic heart function abnormalities (e.g., chronic congestive heart failure) leading to progressive congestive heart failure are the hallmarks of type 2 CRS. In the setting of heart failure, declining renal function is linked to unfavourable outcomes and extended hospital stays. The risk of death is greatly increased by even small reductions in estimated GFR, which is also regarded as a measure of the severity of vascular disease. Acute coronary syndromes, diabetes mellitus, hypertension, and advanced age are independent predictors of declining function. [6]

CRS type 3- Acute Reno-cardiac syndrome: Acute cardiac dysfunction, such as heart failure, arrhythmia, or ischemia, results from an abrupt and primary deterioration of kidney function, such as acute kidney injury (AKI), ischemia, or glomerulo-nephritis, is called acute reno-cardiac syndrome.

CRS type 4- Chronic Reno-cardiac syndrome: A major CKD condition (such as chronic glomerular disease) that contributes to reduced heart function, diastolic dysfunction, ventricular hypertrophy, and/or an elevated risk of adverse cardiovascular events is what defines chronic reno-cardiac syndrome.

CRS type 5- Secondary cardio-renal syndrome: The presence of coupled cardiac and renal dysfunction brought on by acute or chronic systemic diseases is what characterizes type 5 CRS. [7]

CONNECTION BETWEEN HEART FAILURE AND RENAL FUNCTION

Patients with heart failure frequently experience kidney damage as a result of renal ischemia following reduced cardiac output and renal congestion brought on by generalized edema. The association between renal impairment and morbidity and death in people with heart failure is becoming better acknowledged.Patients with kidney disease who experience volume overload

are more likely to develop congestive heart failure. On the other hand, individuals with HF who have poor cardiac output are more likely to experience renal hypo-perfusion and kidney failure.

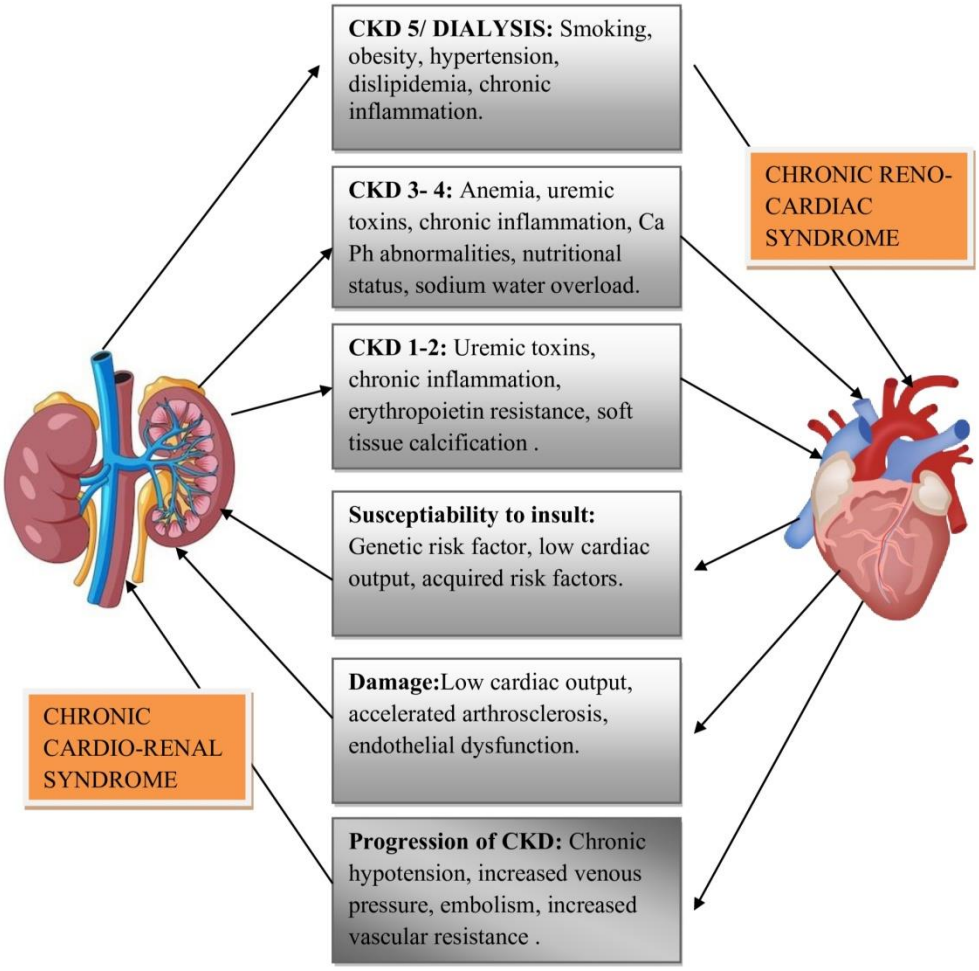

Fig no. 1. Predisposition factor of cardio-renal syndrome image adopted from?

PREDISPOSITION FOR CRS

Hypertension and diabetes mellitus

Most end-stage renal disease and chronic kidney disease (CKD) in wealthy countries are caused by hypertension and type 2 diabetes mellitus. Decreases in GFR and rapid nephron loss are directly linked to hypertension. Diabetes significantly exacerbates chronic kidney disease (CKD) by inducing glomerular dysfunction, damage, and eventual loss of functional filtration units through a variety of processes. Initial evaluations of individuals with ADHF have consistently shown increased blood pressure, perhaps reflecting neuro-hormonal activation and salt retention. [8]

Cardio-metabolic changes and obesity

DM, hypertension, atrial fibrillation, hyperuricemia, heart failure (HF), and chronic kidney disease (CKD) are becoming increasingly common due to obesity. These disorders are either

directly or indirectly linked to excessive body fat. The human body may produce a 10-fold increase in the quantity and size of adipocytes, as evidenced by many studies. Interleukin (IL)-6 and tumor necrosis factor alpha are two cytokines generated by adipocytes linked to heart and kidney illness. [9,10]

Proteinuria

The combination of hypertension and diabetes mellitus causes harm to the endothelium, mesangial cells, and podocytes, which leads to an excess of albumin in Bowman's space and an increased reabsorption burden for the proximal tubular cells. The advancement of kidney disease, further nephron loss, and renal tubular cell death have all been linked to this phenomenon. In fact, the risk of AKI has been repeatedly linked to both albuminuria and extensive proteinuria in many contexts.[11]

Uremic solute retention

Uremia results in myocyte dysfunction, which is characterized by poor calcium transport in the cytosol, which impairs myocyte element contraction. After myocardial infarction, uremia also directly leads to unfavorable remodeling of the heart and hastened fibrosis. Improvements in left ventricular systolic performance, decreases in left ventricular mass, and reductions in left ventricular size have all been linked to the improvement of chronic uremia following kidney transplantation. [12,13]

Anemia

The etiology of anemia in heart failure is complicated and includes hemodilution from water retention, obstruction of normal iron transport, cytokine-induced erythropoietin deficiency brought on by inflammatory processes, tissue resistance, malnourishment, cachexia, and deficiency of vitamins. These factors are all exacerbated in the presence of pre-existing CKD. Elevated hepcidin-25 levels have been linked to decreased erythropoietin responsiveness in HF and CKD patients. Hepcidin-25 is a major regulator that governs iron intestinal absorption as well as distribution across the human body. Increased hepcidin-25 production from the liver, which inhibits the ferroportin receptor and reduces gastrointestinal iron absorption as well as iron production from macrophage and hepatocyte stores, is how high levels of cytokines cause the iron-utilization defect. In individuals with stable chronic heart failure, hepcidin-25 may be helpful in predicting erythropoietin response.[14]

BIOMARKERS OF CRS

A number of biomarkers have been shown to be indicative of the cardiac and renal conditions. According to recent research, there may be a strong correlation between renal function and fibroblast growth factor 23 (FGF23), a hormone that regulates phosphate and is released by osteoblasts. The amount of circulating FGF23 in CKD patients is a significant risk factor for both morbidity and death. FGF23 is a new biomarker that appears to have special properties

due to its primary regulation by renal function and its ability to promote cardiac hypertrophy, according to the mounting data. In distinct ways, FGF23 appears to be involved in the connection between the kidney and the heart. [15]

The hallmark of pre-clinical CRS is endothelial dysfunction, accompanied by restricted acetylcholine-induced endothelium-dependent vasodilatation. Nitric oxide, the bioactive gas that endothelial cells create constitutively, is necessary for endothelial integrity and responsiveness (eNOS). Patients with CKD do, in fact, have lower total NO, which probably reflects lower production and inactivation. The actions of NO that is vasodilator, antithrombotic, anti-adhesive, and anti-inflammatory need bioavailable NO. [3]

PATHOPHYSIOLOGY OF CARDIORENAL RENAL SYNDROME

According to norms, poor renal perfusion—which falls proportionally with decreasing cardiac output—could be the cause of CRS.

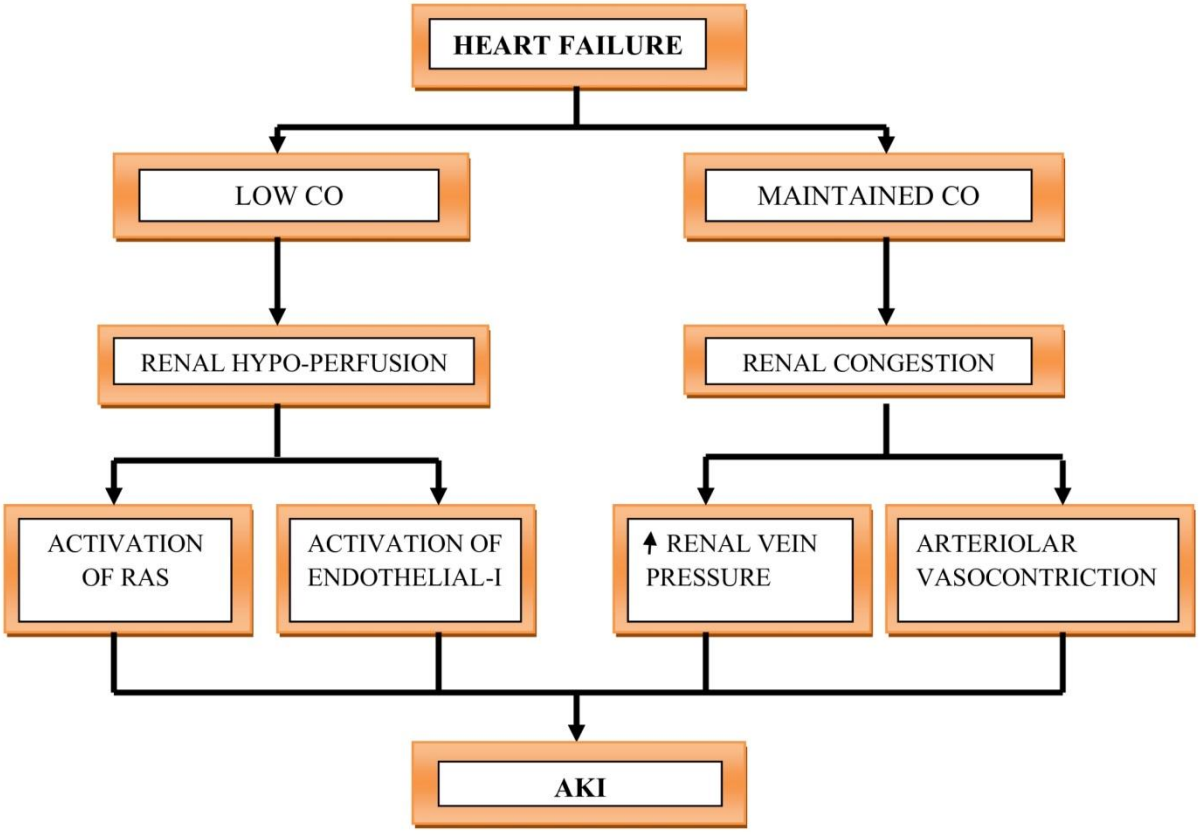

Fig no. 2. Pathophysiology of CRS image adopted from?

Renal impairment in individuals with CRS is mostly caused by elevated central venous pressure (CVP), decreased renal blood flow, and systemic blood pressure, according to a number of investigations.[16] Initially, it has been shown in a number of studies that an increased risk of worsening renal function is associated with higher blood pressure at admission. Conversely, hypotension also results in renal hypoperfusion which is a significant risk factor for worsening renal function. Reduced systemic blood pressure causes the proximal tubule's sodium reabsorption rate to rise, which lowers the amount of sodium at the macula densa. After renin

is secreted as a result of afferent glomerular arterial vasodilation, the RAAS is activated, causing efferent glomerular arterial vasoconstriction. Thus, throughout a broad range of blood pressures, the kidney maintains consistent glomerular capillary pressure, perfusion, and filtration. Nonetheless, in the context of chronic hypertension, a reduced capacity of the preglomerular circulation to dilate in response to a reduction in blood pressure is frequently noted, potentially linked to an amplification of the intraglomerular pressure drop. This justification validates the results showing a hypertension as well as hypotension are linked to an increased risk of renal impairement. [17]

The frequency of AKI was comparable in the Acute Decompensated Heart Failure National Registry amongst HF patients with decreased and intact ejection fraction, suggesting that renal failure in many CRS patients is not likely to be primarily caused by forward flow limitation. Furthermore, individuals with intact ejection fraction have a deterioration in renal function with HF therapy more frequently than patients with substantially reduced ejection fraction. [18,19] The primary pathophysiological mechanism of renal failure in CRS has been identified by recent research as being increased renal backpressure brought on by venous congestion. The backflow of systemic venous congestion results in elevated renal venous pressure, a decrease in the arteriovenous gradient across the renal circulation, and a consequent impairment in renal blood flow. Increased renal venous pressure also causes renal parenchymal congestion within the stiff renal capsule, which in turn raises interstitial pressure and may compress the whole capillary and renal tubules, lowering GFR even in the absence of renal blood flow.[20-22]

TREATMENT OPTION FOR CARDIORENAL SYNDROME

At first, it was thought that decreased cardiac output or a lack of forward flow was the main cause of kidney damage; however, the current theory favours venous congestion as the primary reason for declining renal function. The main approaches of treating cardiorenal syndrome are listed below.

1. INOTROPIC AGENTS

Patients with reduced cardiac output and low blood pressure are frequently treated with inotropic drugs. Medications like milrinone and dobutamine raise cardiac index in proportion to renal blood flow, but there is no conclusive evidence linking these increases to improved clinical outcomes or lower mortality. It is thought that low-dose dopamine, which is frequently used with diuretics, increases renal blood circulation and vasodilatation while attenuating the actions of aldosterone and norepinephrine. It also promotes natriuresis by acting on dopamine-1 and 2 receptors.

2. DIURETICS

The goal of diuretic therapy is to get rid of clinical signs of fluid retention, like peripheral edema and high jugular vein pressure (JVP). It has been discovered that in patients with type I and type II CRS, improvements in cardiac function are linked to improvements in renal

function. The main group of medications used to treat heart failure is called loop diuretics, which include furosemide, bumetanide, torsemide, and ethacrynic acid. Kidney damage may be more likely as a result of their effects on neurohormonal activation, renal, and systemic hemodynamics. [23]

Diuretic resistance is a well-known side effect of using diuretics. It is described as the decrease of the maximal diuretic action, which ultimately limits salt and chloride excretion.Since 95% of loop diuretics are protein bound, hypoalbuminemia makes them less available for facilitated diffusion and increases their volume of distribution. Medications that competitively block diuretics via epithelial cells include uremic toxins and nonsteroidal anti-inflammatory medicines (NSAIDs). Continuous diuretic use can also results in braking phenomena(the reduction of diureticeffect following the successive dosage). [24]

3. ULTRAFILTRATION

During the ultrafiltration procedure, isotonic fluid is eliminated from the blood by passing it through hollow fibers. The ultra filtration composition is in contrast to the reduced salt content of the urine generated by loop diuretics in addition to decongestion. Less potassium waste, lower renin and aldosterone release, and more salt loss are among the possible advantages without the use of loop diuretics.[25] Although the existing data does not support ultrafiltration as the main treatment for efficient decongestion in CRS, it may be beneficial for fluid evacuation in CRS, especially in patients who are not responding to diuretic medication. Rather than adaptive management of ultrafiltration guided by volume assessment, the relative failure of ultrafiltration in comparison to diuretic treatment may have been caused by the set rates of fluid removal. When ultrafiltration treatment is used, a thorough clinical evaluation of the severity of volume overload or venous congestion is crucial. [26]

4. RAAS INHIBITOR

It has been demonstrated that the use of angiotensin-converting enzyme (ACE) and angiotensin II receptor blockers increases the survival rates of heart failure patients and delays the progression of renal impairment. Overdosing or inappropriate treatment regimens can cause hyperkalemia and elevated blood creatinine levels. The increase in dosage of losartan from 50mg to 150mg may decreases the risk of heart failure and prolonged hospitalisation but despite elevate the serum creatinine value and long-term reduction of glomerular filtration rate according to The Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) trial study.[27-28]

5. VASODILATORS AND VASOPRESSOR

Vasodilators lower ventricular filling pressure and CVP, which in turn lowers pulmonary congestion and myocardial oxygen demand. Intravenous nitroglycerin, a common vasodilator, relieves ADHF by lowering venous pressure, which in turn lowers trans-renal perfusion pressure. In their comprehensive study on the functions of vasopressin in heart failure, Vinod

et al. discovered that tolvaptan is a useful short- and long-term treatment for heart failure. Secondary advantages have also been reported, including weight reduction, higher urine production, a return to normal renal function, and elevated serum electrolytes. [29]

CONCLUSION

In conclusion, Cardio-Renal Syndrome represents a complex interplay between heart and kidney dysfunction that poses significant challenges in clinical management. The recognition of this interrelationship is crucial for effective patient care, as both organs can exacerbate each other's conditions, leading to worse outcomes. There is a clear need for more comprehensive research to understand the underlying mechanisms of CRS better and to develop targeted therapeutic strategies. Future studies should also focus on preventive measures that could mitigate the risk of developing CRS in at-risk populations, such as individuals with chronic hypertension and diabetes. By prioritizing multidisciplinary approaches that address both cardiac and renal health, healthcare providers can enhance patient outcomes and reduce the burden of these interconnected diseases.

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