The Egyptian Journal of Hospital Medicine (October 2017) Vol. 69 (6), Page 2730-2735

Congestive Heart Failure in Patients with Chronic Kidney Disease on Dialysis

Saud Mohammed Saeed Alshahrani[1], Saeed Abdulrahman Saleh Alghamdi[1], Ali Saeed Kadasah[1], Mohammed Saeed Kadsah[2], Shubayli Hassan Hayazi Alshehri[1], Sultan Khalid Saeed Kadasah[1], Mohammed Abdullah Mohammed Alqarni[1], Mohammed Sharaf Saad Alshahrani[1], Abdullah Mohammed Hassan Alsuayri[1]

1 King Khalid University, 2 Misr University for Science and Technology

Corresponding Author: Saud Mohammed Saeed Alshahrani - s.semran@hotmail.com - 009665529991886

ABSTRACT

Background: chronic kidney disease can lead to end stage renal disease which would require the patient to be on dialysis. Kidney diseases predispose patients to many complications, such as cardiovascular, hematological, endocrinological, and others. For a patient who is on dialysis, the damaging processes on the cardiovascular system resulting in congestive heart failure are accelerated, making it the biggest cause of mortality. **Methodology:** We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 2001, through February 2017. The following search terms were used: chronic kidney disease, end stage renal disease, congestive heart failure, indications of dialysis, hemodialysis, complications of dialysis, congestive heart failure in dialysis patients. **Aim:** in this review, we aim to evaluate the incidence, prevalence, pathogenesis, and outcome of congestive heart failure in a patient who is on dialysis due to chronic kidney disease. **Conclusion:** Congestive heart failure and chronic kidney disease patients on dialysis have a very bad prognosis of only three years, and there has been no improvement in prognosis from over twenty years. More studies and researches must be conducted in this topic in order to come up with better forms of therapy in order to decrease mortality and improve quality of life.

Keywords: Chronic kidney disease, congestive heart failure, heart failure on dialysis, pathophysiology of congestive heart failure with chronic kidney disease.

INTRODUCTION

Chronic kidney disease (CKD) is a word that covers all degrees of declined renal function. The guidelines have defined CKD as a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for a minimum of 3 months despite of the primary etiology. Kidney disease is the 9th leading cause of death in the United States of America. CKD is classified as stages form 1 to 5 based on the decreasing amount of GFR, where stage 5 is the worst with a GFR <15 mL/min/1.73 m^2, or those requiring dialysis [1]. End stage renal disease (ESRD) is described as a condition of individuals with CKD, who necessitate renal replacement therapy. There are two types of renal replacement therapy, which are dialysis or transplant. ESRD is the most dreaded complication of CKD [2]. Indications for renal replacement therapy comprise presence of any of the following: severe metabolic acidosis, hyperkalemia, intractable volume overload, encephalopathy, pericarditis, failure to thrive and malnutrition, peripheral neuropathy, intractable gastrointestinal symptoms, and in asymptomatic patients with a GFR of 5-9 mL/min/1.73 m². The listed conditions are irrespective of the cause of the CKD or the presence or absence of other comorbidities [3].

The typical life expectancy of a patient on hemodialysis is less than 3 years, and unfortunately, hasn't changed in over 20 years [2]. CKD is associated with an increased risk of developing cardiovascular disease, chronic renal failure, hypertension, anemia, protein loss, platelet dysfunction, fatigue, and overall decreased quality of life. Cardiovascular disease remains the greatest cause of mortality in patients with ESRD, and it accounts for 53% of all deaths with a known cause in dialysis patients. It is assessed that up to 36% of all people with ESRD already have congestive heart failure (CHF) at the beginning of dialysis, while another 25% of dialysis patients progress to de-novo CHF. The yearly incidence of such occurrence is 7% [4]. The patho-biological processes that reinforce the severity and advancement of cardiovascular disease in CKD include hastened atherosclerosis and constant reduction in the function of left ventricular (LV) as the renal function declines, and when that patient is on hemodialysis, these processes are accelerated [3].

Received: /08/2017
Accepted: /08/2017

DOI: 10.12816/0042256

In this review, we aim to evaluate the incidence, prevalence, pathogenesis, and outcome of congestive heart failure in a patient who is on dialysis due to chronic kidney disease.

METHODOLOGY

- **Data Sources and Search terms**

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 2001, through February 2017. The following search terms were used: *chronic kidney disease, end stage renal disease, congestive heart failure, indications of dialysis, hemodialysis, complications of dialysis, congestive heart failure in dialysis patients*

- **Data Extraction**

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the Ethics Board of **King Khalid** University.

DISCUSSION

CHF is a very common condition in the common population. Currently it affects 23 million across the world [4]. There are many risk factors for CHF, namely coronary artery disease, male gender, obesity, and hypertension. The most common conditions associated with CHF are aging, hypertension, diabetes mellitus, Left ventricular hypertrophy (LVH), coronary artery disease, and infiltrative cardiomyopathy, which are all common comorbidities CKD patients [5]. Those comorbidities are associated with the initiation and worsening of myocardial fibrosis and reduced ventricular compliance. Subclinical heart failure and left ventricular hypertrophy (LVH) is the most common echocardiographic finding in CKD patients on hemodialysis [6].

HF is also a very common presentation in patients with CKD. On the other hand, uncontrolled CHF also very commonly causes progression of renal failure. This creates a vicious cycle where CHF can be the cause of renal failure, and renal failure can worsen the CHF even further by directly affecting the heart [3]. Recent animal studies have suggested that abnormal cardiac function contributes significantly to advanced loss of kidney function [7]. CHF and CKD act synergistically in causing renal damage. The mortality rate and going on to dialysis therapy increases by 50–100% when CHF and CKD present together [8].

It is estimated that 50% of the patients with CHF have CKD. Also it is worth noting that CHF was 15.1 times more prevalent in those with CKD compared to those with normal kidney function. The prevalence of CHF increases as the renal function worsens. Therefore, CKD is a powerful and independent risk factor for cardiovascular diseases. In the US, for instance, the prevalence of cardiovascular diseases in CKD patients is as high as 63%, while only 5.8% in people without CKD. Additionally, the prevalence is directly linked with the severity of CKD [3].

Congestive Heart Failure in Chronic Kidney Disease- Interrelated Pathophysiology.

The significant link between CKD and cardiovascular diseases is explained by the typical overlapping of numerous risk factors [9]. These risk factors are classified as

-*traditional*: advanced age, hypertension, diabetes, and dyslipidemia and

-*nontraditional*: CKD-specific factors such as anemia, volume overload, proteinuria, malnutrition, metabolism abnormalities, inflammation, and oxidative stress.

CHF is associated with a reduction in renal blood flow and GFR. Proteinuria many times can occur in CHF and damages the kidneys. These factors which are triggered by ischemia, including the cytokines produced, lead to the damage of glomerulus, mesangium, tubular cells and interstitial cells, along with progressive fibrosis [10]. This causes progressive renal ischemia which also activates renin-angiotensin-aldosterone system and sympathetic activity leaving toxic effects on the renal tissue. High amount of angiotensin II can collect in the heart and lead to myocyte hypertrophy, fibrosis of interstitium, and microvascular ailment, disturbance in cardiac conduction system, prolonged QT, and eventually arrhythmias [11]. High aldosterone in the serum can induce fibrosis of myocardium, assumed to be due to the release of transforming growth factor β [12].

CKD reversely deteriorates CHF. The rise in serum creatinine level is one of the best forecasters of mortality in CHF. The changes that take place in the uremic heart are outlined below [10]:

(1) Atherosclerotic plaques grow quicker in a uremic environment. High blood urea occurs early in renal disease.
(2) There is a deficient micro-vessel growth compared to the hypertrophy of cardiomyocytes. This makes the myocytes deprived of oxygen supply. Ischemia stimulates myocardial cell apoptosis, as well as accumulation of extracellular matrix and collagen, resulting in interstitial fibrosis. Fibrosis promotes LV stiffness, increased filling pressure of the LV, weakened diastolic filling, and eventually diastolic dysfunction. Myocardial fibrosis additionally worsens ischemia by reducing the capillary density and reserve, and considerably increases the risk of ventricular arrhythmias and sudden cardiac death [9; 13]. Associated coronary artery disease—also, very common in patients with CKD and ESRD—further contributes to ischemia, myocardial cell damage, and fibrosis. Myocardial fibrosis aggravates ischemia, by reduction of capillary density and coronary reserve system. Fibrosis also considerably upsurges the possibility of ventricular arrhythmias and sudden cardiac death [13]. Concomitant coronary artery disease, which is also very commonly found in patients with CKD and ESRD, contributes to ischemia, further cell damage, and fibrosis [11].
(3) The coronaries fail to vasodilate as a result of endothelial dysfunction.
(4) Studies of the metabolism of the heart in uremia have shown a decay of energy-rich nucleotides, especially ATP [14]. Thus, there is a reduction in energy stores.
(5) The sympathetic activity is amplified and so is the apoptosis. In response, the chemoreceptors and baroreceptors in the already damaged kidney are activated causing further load on the heart by increasing the heart rate and contraction, predisposing it to development of arrythmias. Apoptosis happens due to disproportionate sympathetic activity of the cardio muscles. Sympathetic overactivity may even induce concentric remodeling of the LV [15].
(6) Uremia leads to several abnormalities of cardiac muscle function, including the abnormal calcium cycle affecting its contractile function. Deficiency of vitamin D is commonly seen in CKD patients, and is linked with myocardiac hypertrophy. It is related to early cardiovascular mortality as well as sudden cardiac death in patients on dialysis. It has been well recognized that vitamin D has a number of biological effects on the heart, such as cardiac cell contraction, hypertrophy, proliferation, differentiation, and protein and collagen expression of cardiac muscles. Furthermore, vitamin D plays a role in the maintenance of tone of vessels and cardiac output [16].

Congestive Heart Failure with Dialysis

In dialysis-dependent ESRD patients, the risk of cardiovascular mortality is 10-fold to 20-times higher than in any other age- and gender-matched control subjects without associated chronic kidney disease [17]. Patients with CHF have an additional struggle in tolerating certain kinds of hemodynamic stress, for instance, atrial fibrillation, tachycardia, changes in blood pressure, and ischemia-induce acute presentation of or deterioration of diastolic dysfunction [18]. At the same time, these causes of hemodynamic stress are particularly frequent in patients with CKD, especially those on hemodialysis. Dialysis patient are hemodynamically at a hypervolemic state due to high blood flow through the arterio-venous fistula leading to volume overload which consequently leads to LV dilatation (eccentric left ventricular hypertrophy), by buildup of new myocardial fibers in series [19].

The median survival of dialysis-dependent patients with baseline heart failure is estimated to be 3 years, in contrast with 5 years for those without baseline heart dysfunction. Over 80% of ESRD patients who are recently diagnosed with HF are expected to die within only three years from the time of this diagnosis. It is evaluated that up to 36% of all people with ESRD already have CHF at the beginning of dialysis, while another 25% of dialysis patients progress to de-novo CHF. The yearly incidence of such occurrence is 7% [20].

Anemia as a Worsening Factor

To further add to this vicious cycle of CHF and CKD is anemia, which itself is a product of CKD and CHF. At the same time anemia worsens both CHF and CKD. This vicious cycle can be called the cardio-renal-anemia syndrome. Intervention of CHF and anemia can help prevent the progression of CHF as well as CKD [21]. About 40–50% of patients with CHF have anemia. Anemia has many causes in this case, but the two most significant ones are possibly CKD itself and cytokine-induced depression of production of erythropoietin along with depression of bone marrow use of the available erythropoietin. The cytokine tumor necrosis factor beta is existent in

increased concentrations in the blood of CHF patients [22]. They can act to depress red blood cell formation. Many studies found that the severity of anemia was proportional to the severity of CHF, additionally causing higher mortality, and increased need for hospitalization. Therefore, it appears that treatment of anemia in CKD is helpful in preventing CHF. There is some suggestion that improvement of anemia is connected with both a slowing the advancement of the renal failure and also delaying the time to onset of dialysis [23].

A study was conducted on 179 patients with severe, resistant CHF and who were also anemic. They were not responsive to maximally tolerated doses of ACE inhibitors and beta blockers until the underlying anemia was corrected erythropoietin subcutaneously along with intra-venous iron (iron sucrose-Venofer). The CHF was then noted to be improved, and their rate of hospitalization and oral or intravenous diuretics doses fell. In 80% of the cases, the creatinine clearance surprisingly increased, or stayed the same [21].

From a hemodynamic view, left ventricular hypertrophy is an adaptive remodeling process of LV, which is necessary to compensate the increase in cardiac work. The increased work is caused by an increase in afterload (pressure overload), an increase in preload (volume overload), or both. Increase in afterload may be a consequence of arterial hypertension, wall stiffness, or stenosis of aortic valve [23]. This leads to a concentric thickening of the LV wall in a concentric fashion. High preload may be due to high volume, anemia, and dialysis patient high blood flow through the arterio-venous fistula leading to volume overload which consequently leads to LV dilatation (eccentric left ventricular hypertrophy), by buildup of new myocardial fibers in series [19].

Diagnosis of Congestive Heart Failure in Chronic Kidney Disease

The American College of Cardiology Foundation/American Heart Association, the Heart Failure Society of America and the European Society of Cardiology recommend the following basic laboratory tests and studies in the initial evaluation of patients with suspected heart failure [24]:

- Complete blood count
- Urinalysis, which can reveal proteinuria
- Serum electrolyte levels, which may be abnormal owing to causes such as fluid retention or renal dysfunction [10]
- Blood urea nitrogen and creatinine levels, which may show diminished renal blood flow as well as declining renal function [25]
- Fasting blood glucose levels as elevated levels show an increased risk for heart failure (including in non-diabetic patients)
- Liver function tests, which can reveal elevated liver enzyme levels and show liver dysfunction as a result of heart failure
- B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide levels, which are elevated in heart failure [26]
- a 12-lead electrocardiogram, which can show arrhythmias, ischemia, infarction, or coronary artery diseases
- Chest radiography (posterior-anterior, lateral), which reveals pulmonary congestion or enlarged heart chambers [27]
- Two-dimensional echocardiographic and Doppler flow ultra-sonographic studies, which may tell about ventricular dysfunction and chamber enlargement
- Coronary arteriography to detect if any ischemic LV dysfunction is present [28]

Assessment of fluid status is very crucial in all CKD and, above all, in ESRD patients. In those patients with CKD and CHF, volume overload may be both a result and a triggering factor of the concluding condition [29].

Treatment of Heart Failure in Chronic Kidney Disease

The main aims of CHF therapy in CKD patients are:

-to decrease both the preload and afterload which eventually reduces LVH,

-to treat myocardial ischemia if present, and

-to inhibit the sympathetic nervous system and the renin-angiotensin-aldosterone system [30]

Strategies to minimize large volume shifts with the help of high-dose loop diuretic, salt and water restriction, and frequent dialysis is crucial. Dietary salt restriction and diuretics are endorsed for CKD and CHF patients to strictly control fluid overload and its symptoms. Loop diuretics are used as first-line drugs in patients with a GFR <30 mL/min/1.73 m^2 [1]. In patients with CKD and ESRD also have anemia, therefore, it should be treated as per to the guidelines used in the general CKD population. Serum hemoglobin of 11 to

12 g/dL should be the target. Vitamin D deficiency and low phosphate levels are concomitant with LV hypertrophy and dysfunction [31]. A satisfactory phosphate, calcium, vitamin D, and PTH level is a goal in CKD patients. In CKD patients with CHF, beta-blockers have shown to reduce mortality and hospitalization. Hence, a beta-blocker should be advised to all such patients, unless contraindicated. Treatment must be initiated at a very low dose and carefully increased and monitored the entire time to prevent worsening heart failure, hypotension, and bradycardia especially in dialysis patients [32].

Studies have revealed a promising effect of ACEIs on survival in patients with CKD and CHF; however, patients with serum creatinine >2.5 mg/dL were not a part of those trials. Unfortunately in patients with HF and ESRD, the ACE inhibitors have shown higher risk of adverse events. ARBs can be used, particularly in patients who develop cough or angioedema from ACEIs. RAAS inhibitors require cautious dose titration and monitoring in order to prevent serious adverse effects, like drop in blood pressure, hyperkalemia, and acute kidney injury. In stage 3 CKD subjects with heart failure, aldosterone antagonists should be used with a lot of caution, with close monitoring of the levels of potassium [25].

For ESRD patients with CHF adequate ultrafiltration is crucial for controlling volume overload. In hemodialysis, large-volume ultrafiltration must be avoided, as it can cause myocardial stunning episodes. High-flow A-V fistula should also be avoided because it adds to volume overload, increased cardiac output, and eccentric left ventricular hypertrophy. Instead, short daily or long nocturnal dialysis result in better fluid status [25]. To improve clinical outcomes of dialysis patients with heart failure, the therapeutic goal must be to [33]:

(1) recover hemodynamics by reducing both preload and afterload by treatment of hypertension, curing hypervolemia and arterial hardening, and lessening the positive sodium balance
(2) treat cardiac ischemia
(3) decrease LV hypertrophy and fibrosis
(4) inhibit the sympathetic nervous system

Blood pressure control is crucial and has favorable effects in CKD and ESRD patients. It leads to regression of left ventricular hypertrophy and improves diastolic function [34]. Candesartan use in hemodialysis patients has significantly decreased cardiovascular mortality, perhaps due to regression on myocardial fibrosis [35].

CONCLUSION

We have seen the significant inter-related pathophysiology of CHF with CKD and its worsening nature with ESRD or on patients who are receiving dialysis therapy. These concomitant conditions affect a vast population and unfortunately, have a very bad prognosis of only three years. What is worse is that there has been no improvement in prognosis from over twenty years. Therefore, more studies and researches must be conducted in this topic in order to come up with better forms of therapy to decrease mortality and improve quality of life.

Refrences

1. **Rule AD, Amer H, Cornell LD *et al*. (2010):** The association between age and nephrosclerosis on renal biopsy among healthy adults. Ann Intern Med., 152: 561–567.
2. **Wen C P *et al.* (2014):** Relative risks of chronic kidney disease for mortality and end-stage renal disease across races are similar. Kidney Int., 86: 819-827.
3. **Ahmed A, Campbell R C (2008):** Epidemiology of chronic kidney disease in heart failure. Heart Fail Clin., 4: 387-399.
4. **Saito M, Wright L, Negishi K, Dwyer N, Marwick T H (2017):** Mechanics and prognostic value of left and right ventricular dysfunction in patients with systemic sclerosis. Eur Heart J Cardiovasc Imaging, doi: 10.1093/ehjci/jex147.
5. **Kim M S *et al.* (2017):** Korean Guidelines for Diagnosis and Management of Chronic Heart Failure. Korean Circ J., 47: 555-643.
6. **Senni M *et al.* (2014):** New strategies for heart failure with preserved ejection fraction: the importance of targeted therapies for heart failure phenotypes. Eur Heart J., 35: 2797-2815.
7. **Pawlaczyk K, Baum E, Schwermer K, Hoppe K, Lindholm B, and Breborowicz A (2015):** Animal Models of Peritoneal Dialysis: Thirty Years of Our Own Experience. Biomed Res Int., http://dx.doi.org/10.1155/2015/261813
8. **Dhingra R, Gaziano J M, Djousse L (2011):** Chronic kidney disease and the risk of heart failure in men. Circ Heart Fail, 4: 138-144.
9. **Shah R *et al.* (2015):** Serum Fractalkine (CX3CL1) and Cardiovascular Outcomes and Diabetes: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis., 66: 266-273.

10. **Sandsmark D K *et al.* (2015):** Proteinuria, but Not eGFR, Predicts Stroke Risk in Chronic Kidney Disease: Chronic Renal Insufficiency Cohort Study. Stroke, 46: 2075-2080.
11. **Townsend R R (2015):** Arterial stiffness and chronic kidney disease: lessons from the Chronic Renal Insufficiency Cohort study. Curr Opin Nephrol Hypertens., 24: 47-53.
12. **He J *et al.* (2017):** Risk Factors for Heart Failure in Patients With Chronic Kidney Disease: The CRIC (Chronic Renal Insufficiency Cohort) Study. J Am Heart Assoc., doi: 10.1161/JAHA.116.005336.
13. **Dienemann T *et al.* (2016):** International Network of Chronic Kidney Disease cohort studies (iNET-CKD): a global network of chronic kidney disease cohorts. BMC Nephrol., 17: 121.
14. **Nikolaidou T *et al.* (2015):** Congestive Heart Failure Leads to Prolongation of the PR Interval and Atrioventricular Junction Enlargement and Ion Channel Remodelling in the Rabbit. PLoS One, 10: e0141452. doi.org/10.1371/journal.pone.0141452
15. **Kaur J, Young B E Fadel PJ (2017):** Sympathetic Overactivity in Chronic Kidney Disease: Consequences and Mechanisms. Int J Mol Sci., 18: 1862.
16. **Chau Y Y, Kumar J (2012):** Vitamin D in chronic kidney disease. Indian J Pediatr., 79: 1062-1068.
17. **Pecoits-Filho R, Bucharles S and Barberato S H (2012):** Diastolic heart failure in dialysis patients: mechanisms, diagnostic approach, and treatment. Semin Dial., 25: 35-41.
18. **Brisco M A, Testani J M (2014):** Novel renal biomarkers to assess cardiorenal syndrome. Curr Heart Fail Rep., 11: 485-499.
19. **Peiskerova M *et al.* (2013):** Placental growth factor may predict increased left ventricular mass index in patients with mild to moderate chronic kidney disease--a prospective observational study. BMC Nephrol., 14: 142.
20. **Sarnak M J (2014):** A patient with heart failure and worsening kidney function. Clin J Am Soc Nephrol., 9: 1790-1798.
21. **Kurella Tamura M *et al.* (2016):** Anemia and risk for cognitive decline in chronic kidney disease. BMC Nephrol., 17: 13.
22. **Shah R, Agarwal A K (2013):** Anemia associated with chronic heart failure: current concepts. Clin Interv Aging, 8: 111-122.
23. **Sandhu A, Soman S, Hudson M, Besarab A (2010):** Managing anemia in patients with chronic heart failure: what do we know? Vasc Health Risk Manag., 6: 237-252.
24. **Wouters O J, O'Donoghue D J, Ritchie J, Kanavos PG, Narva A S (2015):** Early chronic kidney disease: diagnosis, management and models of care. Nat Rev Nephrol., 11: 491-502.
25. **Segall L, Nistor I, Covic A (2014):** Heart failure in patients with chronic kidney disease: a systematic integrative review. Biomed Res Int., 2014: 937398.
26. **Mishra RK *et al.* (2013):** Association of N-terminal pro-B-type natriuretic peptide with left ventricular structure and function in chronic kidney disease (from the Chronic Renal Insufficiency Cohort (CRIC)). Am J Cardiol., 111: 432-438.
27. **Tovar M, Rodriguez M R (2017):** Acquired heart disease in adults: what can a chest X-ray tell us? Radiologia, 59: 446-459.
28. **Silverberg D, Wexler D, Blum M, Schwartz D, Iaina A (2004):** The association between congestive heart failure and chronic renal disease. Curr Opin Nephrol Hypertens., 13: 163-170.
29. **Ricardo AC *et al.* (2015):** Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis., 65: 412-424.
30. **Kelly TN *et al.* (2015):** The role of renin-angiotensin-aldosterone system genes in the progression of chronic kidney disease: findings from the Chronic Renal Insufficiency Cohort (CRIC) study. Nephrol Dial Transplant, 30: 1711-1718.
31. **Zhou C, Wang F, Wang J W, Zhang LX, Zhao M H (2016):** Mineral and Bone Disorder and Its Association with Cardiovascular Parameters in Chinese Patients with Chronic Kidney Disease. Chin Med J (Engl), 129: 2275-2280.
32. **Chang TI, Yang J, Freeman J V, Hlatky M A (2013):** Effectiveness of beta-blockers in heart failure with left ventricular systolic dysfunction and chronic kidney disease. J Card Fail, 19: 176-182.
33. **Gurwitz J H *et al.* (2017):** Treatment Effectiveness in Heart Failure with Comorbidity: Lung Disease and Kidney Disease. J Am Geriatr Soc., doi: 10.1111/jgs.15062
34. **Cheung A K *et al.* (2017):** Effects of Intensive BP Control in CKD. J Am Soc Nephrol., 28: 2812-2823.
35. **Mills K T *et al.* (2016):** Sodium Excretion and the Risk of Cardiovascular Disease in Patients With Chronic Kidney Disease. JAMA., 315: 2200-2210.