

Chronic Kidney Disease and Cardiovascular Disease: Pathophysiologic Links

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The American Heart Association has recognized patients with chronic kidney disease (CKD) as having the highest risk for development of cardiovascular disease (CVD). Individuals undergoing dialysis were recognized as having an accelerated rate of atherosclerosis as early as 1974 (Lindner, Charra, Sherrard & Scribner, 1974). Foley, Parfrey, and Sarnak (1998) quantified that risk, noting that patients on dialysis have a 10 to 30 times greater CVD mortality compared to age-matched individuals in the general population. Cardiac disease has been recognized as the leading cause of death in patients on dialysis with 45% attributed to CVD (Foley et al., 1998). More recently, it has become apparent that this increase in cardiovascular risk begins in the early stages of CKD (Amann et al., 2003). There are a myriad of CVD risk factors seen in patients with CKD. Risks are classi-

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This is the second in a series of three articles about the risk factors and complications related to chronic kidney disease and their impact on cardiovascular disease. This article focuses on identifying pathophysiologic mechanisms by which two traditional risk factors of cardiovascular disease (hypertension and dyslipidemia), and two nontraditional risk factors associated with chronic kidney disease (anemia and abnormalities in bone and mineral metabolism) contribute to the markedly increased cardiovascular morbidity and mortality seen in individuals with chronic kidney disease.

Goal

Identify pathophysiologic mechanisms by which risks factors for cardiovascular disease contribute to the increased cardiovascular morbidity and mortality seen in individuals with chronic kidney disease (CKD).

Objectives

1. Describe the villain-victim development of hypertension in patients with CKD.
2. Identify dyslipidemias seen in patients with CKD.
3. Discuss anemia and its contribution to development of left ventricular hypertrophy (LVH).
4. Describe the development of arterial stiffness in patients with CKD.

fied as classic or traditional risk factors common in many adults, but also additional CKD-related risks that contribute to CVD (see Table 1). In this article, the classic risk factors of hypertension and dyslipidemia as well as the CKD-related risk factors of anemia and abnormalities in bone and mineral metabolism will be reviewed. The pathophysiologic mechanisms by which these risk factors are linked to CVD in the patient

population with CKD will be discussed.

Hypertension

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure notes that the relationship between blood pressure (BP) and CVD "is continuous, consistent, and independent of other risk

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Table 1
Cardiovascular Risk Factors in Adults with CKD

Traditional	CKD Related
Older age	Decreased GFR
White race	Proteinuria
Male gender	Peripheral renin-angiotensin-aldosterone activity
Hypertension	Anemia
Increased LDL cholesterol	Abnormal calcium and phosphorus
Decreased HDL cholesterol	Hypoalbuminemia
Diabetes Mellitus	Hemodynamic overload
Tobacco Use	Thrombogenic factors
Physical Inactivity	Hyperhomocysteinemia
Obesity	Chronic inflammation
Physical inactivity	
Psychosocial stress	
Positive family history of CVD	
LVH	

Source: Adapted from Mitsnefes (2005).

Table 3
Factors Associated with Development of Acceleration or Valvular Calcification in Patients on Dialysis

General Population	CKD Related
Advancing age	Vascular calcification
Systemic hypertension	Hyperphosphatemia
Diabetes Mellitus	Hypercalcemia
Abnormal lipids	Elevated PTH levels
LVH	Elevated calcium and phosphorus product

Source: Data from Cunningham, Corretti, and Henrich (2006).

factors. The higher the BP, the greater the chance of MI, heart failure (HF), stroke and kidney disease” (Chobanian et al., 2003, p. 2562). Lowering BP reduces the incidence of these events (see Table 2). In individuals with evidence of target organ damage (changes in the retina, brain, heart, kidneys, or large conduit arteries), achieving a sustained reduction of only 12 mmHg in the systolic BP for 10 years will prevent 1 death for every 9 patients treated (Chobanian et al., 2003). It is apparent that uncontrolled hypertension is a cardiovascular killer.

Hypertension is common in individuals with CKD, with the prevalence increasing as glomerular filtra-

tion rate (GFR) decreases (National Kidney Foundation [NKF], 2002). More specifically, data from the Modification of Diet in Renal Disease Study showed that the prevalence of hypertension rose from 65% to 95 % as the GFR declined from 85 to 15 mL/min per 1.73 m² (Buckalew et al., 1996). Elevated systolic BP was an independent risk factor for CVD outcomes, with a 1.35-times greater risk of CVD events requiring hospitalization for every 10 mmHg increase in systolic BP (Buckalew et al., 1996).

Hypertension and CKD are linked in what has been termed a villain-victim relationship, referring to the potential two-way causality (Marin, Gorostidi, Fernandez-Vega, &

Table 2
Benefits of Lowering Blood Pressure

Event	% Risk Reduction
Stroke	35-40
Myocardial Infarction	20-25
Heart Failure	50

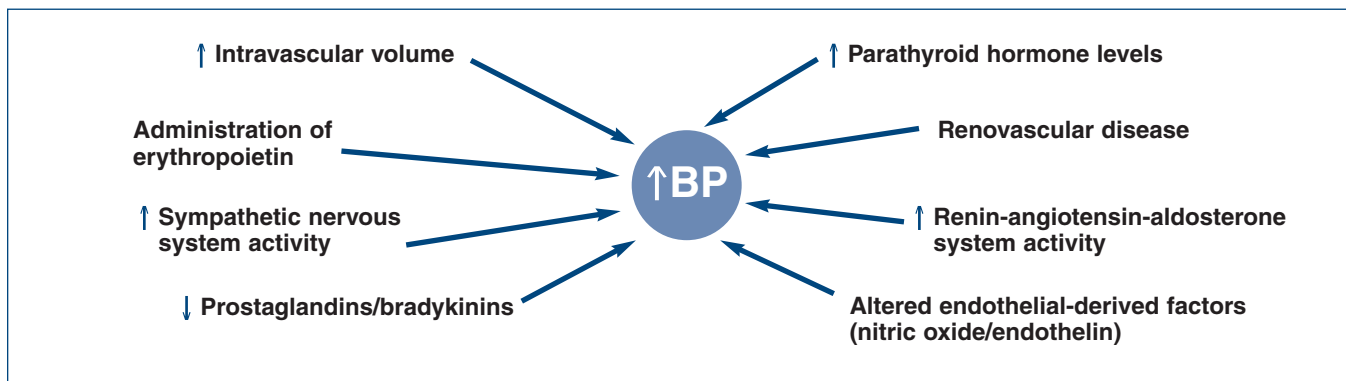
Source: Data from Chobanian et al. (2003).

Alvarez-Navascues, 2005). Many primary kidney diseases can cause hypertension, but hypertension also contributes to the development and progression of kidney disease, forming a cycle of deterioration. Thus, treatment of hypertension is paramount to slowing the progression of CKD, and also to mitigating the damage done to target organs. Figure 1 summarizes several major contributors of CKD to development or progression of hypertension.

Hypertension is often associated with the development of CKD, especially if it is poorly controlled. In patients with both CKD and hypertension, impaired renal autoregulation results in the transmission of elevated systemic pressure to the glomerulus with damage to glomerular cells, ultimately resulting in sclerosis. This glomerular hypertension leads to endothelial, mesangial, and epithelial injury in the kidney (Kaplan, 2006). Uncontrolled hypertension results in higher pressures being transmitted to the glomerulus, increasing the risk for further damage. This has prompted the Joint National Committee on High Blood Pressure (Chobanian et al., 2003) and the National Kidney Foundation (2004) to recommend a BP goal of less than 130/80 mmHg in patients with CKD. Volume expansion related to the inability of the diseased kidney to handle salt and water appropriately is a primary contributor to hypertension in patients with CKD (Kaplan, 2006). Initiation of dialysis in advanced CKD will significantly lower the BP in 80% of patients (Augustyniak,

Figure 1

Overview of major factors that contribute to development or worsening of hypertension in patients with CKD. Elevated blood pressure also contributes to further structural injury to the kidney and progressive kidney disease (Kaplan, 2006).



Tuncel, Zhang, Toto, & Victor, 2002).

There is evidence of sympathetic overactivity in patients with CKD, with increased catecholamines contributing to a rise in BP. The failing kidneys are thought to be the source, since this effect is not seen in patients who have undergone bilateral nephrectomies (Neumann, Ligtenberg, Klein, Koomans, & Blankestijn, 2004). It has been hypothesized that sympathetic overactivity is dependent upon activation of the renin-angiotensin-aldosterone system (RAAS), since a decrease in renal arteriolar pressure as well as an increase in renal nerve activity stimulates renin release. Augustyniak et al. (2002), in their review of the literature, conclude that sympathetic overactivity in uremia may be caused by a neurogenic signal from the renal afferents of the failing kidney. A small prospective study by Ligtenberg et al. (1999) of patients with CKD (pre-dialysis) seems to support this idea. This study concluded that enalapril monotherapy, an inhibitor of the RAAS, normalized BP and muscle sympathetic nerve activity. Since this abnormality is present in patients with CKD prior to dialysis, it is clearly not a consequence of the dialysis treatment. "In addition, in patients with chronic renal insufficiency and renin-dependent hypertension, sympathetic overactivity was normalized by chronic angiotensin converting

enzyme inhibition but not by calcium channel blockade, implicating a major central neural action of angiotensin II" (Augustyniak et al., 2002, p. 3). In theory, sympathetic overactivity could have direct effects on cardiac and vascular smooth muscle that contribute to additional target organ damage (Augustyniak et al., 2002). More data are needed to confirm these findings and clarify the nature of the relationship between the RAAS and sympathetic overactivity.

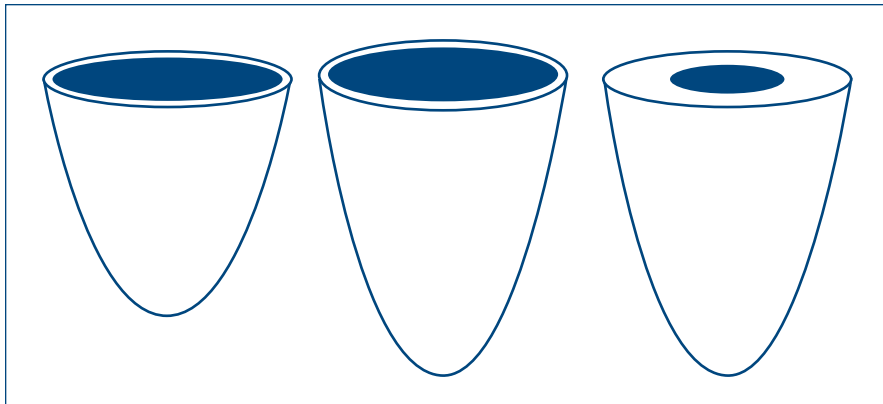
Ischemia-induced activation of the RAAS in patients with CKD results in increased levels of angiotensin II. Renal ischemia is exacerbated by nephrosclerosis and scarring of the glomerulus. The high levels of angiotensin II result in increases in intracellular sodium and calcium, leading to vasoconstriction and elevated BP (Morse, Dang, Thakur, Zhang, & Reisin, 2003). Primary vascular disease such as renal artery stenosis, or small vessel disease with resultant regional ischemia contributes to stimulation of the RAAS (Morse et al., 2003). Aldosterone excess can lead to vascular damage in the form of endothelial stiffness and fibrosis of both the heart and the kidney, directly contributing to both CVD and CKD (Kaplan, 2006).

Hypertension can contribute to changes in the structure and function of the heart, specifically the left ven-

tricle. Left ventricular hypertrophy (LVH) refers to the adaptation of the myocardium to increased cardiac load. Volume overload, pressure overload, or both can contribute to LVH. In its initial stages, LVH is an adaptive process and can be normal with growth maturation, pregnancy, and high level exercise (Kaplan, 2006). It is helpful in that the increase in the number of functional cardiac muscle units (sarcomeres) allows for the distribution of the load and maintenance of normal systolic function. However, sustained overload becomes progressively maladaptive and can result in cardiomyopathy and heart failure (HF) (London, 2003a). Concentric LVH refers to an increase in wall thickness but without a simultaneous increase in volume capacity, generally caused by pure BP overload (Kaplan, 2006). Eccentric hypertrophy is an increase in volume capacity of the chamber or chamber enlargement, but not relative wall thickness. Eccentric hypertrophy is associated with increased diastolic stress, whereas concentric hypertrophy relates to increased systolic stress (London, 2003a) (see Figure 2). The presence of LVH can be diagnosed by electrocardiogram or echocardiography, but echocardiography is preferred since it has a higher sensitivity.

Left ventricular mass is indexed for body size and reported as grams

Figure 2
This illustration represents, from left to right, a normal left ventricle, eccentric left ventricular hypertrophy, and concentric left ventricular hypertrophy.



per meter squared. LVH results in an increase in left ventricular mass, whether the LVH is concentric, eccentric, or a combination of both forms. The prevalence of LVH in patients with CKD is high in all age groups (even children), begins early in CKD, and progresses as renal function declines. Levin, Singer, Thompson, Ross, and Lewis (1996) noted the existence of LVH in 30% to 45% of patients with CKD who were not on dialysis with a higher prevalence and increasing severity as kidney function declines. London (2003a) noted that 75% of adults and 69% of pediatric patients have LVH at initiation of dialysis. More recently, Pendse and Singh (2005) noted that a paltry 15% of patients have normal left ventricular function at the initiation of dialysis. LVH is a poor prognostic finding, with a host of associated adverse effects, including HF, ventricular arrhythmias, sudden cardiac death, death following MI, decreased LV ejection fraction, and cerebrovascular events (Berns, 2006a).

Pressure overload can be from hypertension, arteriosclerosis, aortic stenosis, or any combination of these factors. Stiffness of the aorta and large central arteries, as well as increased peripheral vascular resistance, increases the work load of the left ventricle, contributing to LVH early

in renal disease. The arterial stiffness results in an increase in the pulse wave velocity and subsequent early return of wave reflections, generating additional pressure to oppose LV ejection (London, 2003a). Likewise, hemodynamically significant aortic stenosis creates obstruction to LV ejection, contributing to LVH. Volume overload in CKD is common, and also contributes to LVH.

Although outside the scope of this review, proteinuria has been identified as an independent risk factor for both CVD and progression of CKD. It is seen in both diabetic and nondiabetic forms of CKD. Use of antihypertensive agents designed to block to RAAS such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are recommended to control BP and minimize proteinuria in individuals with hypertension and CKD (Chobanian et al., 2003).

Dyslipidemia

The link between dyslipidemia and CVD in the general population has been substantiated in the literature. The significance of lipid abnormalities in CKD has been less well-defined. There is evidence to suggest that once injury to the kidneys has occurred, lipid abnormalities may

hasten the progression of CKD (Keane & Lyle, 2005). Dyslipidemias have been demonstrated to be one of the risk factors contributing to “the greater rate of cardiovascular morbidity and mortality among CKD patients [when compared to] the general population” (Bianchi, Bigazzi, Caiazza, & Campese, 2003, p. 565). Surprisingly, lipid-lowering medications such as statins are not widely used in patients with CKD (Fathi et al., 2004).

Dyslipidemia can occur early in CKD and can worsen as overall kidney function declines. Multiple factors can play a part in determining the pervasiveness of dyslipidemia in CKD, including the type of underlying kidney disease, level of kidney function, presence of diabetes, and use of particular pharmacotherapy such as cyclosporine or corticosteroids (Agarwal & Curley, 2005). Multiple types of lipid abnormalities are present in CKD: (a) elevated total cholesterol, (b) elevated triglycerides, (c) increased LDL cholesterol, and (d) low HDL cholesterol. Individuals with nephrotic syndrome (proteinuria greater than 3.5 grams in 24 hours) tend to have high total cholesterol and elevated LDL, though total to be due to the combination of increased production and decreased catabolism of lipoproteins. Hypertriglyceridemia in these patients is thought to be caused by decreased catabolism of the triglycerides. Patients with stages 2-4 CKD who are not nephrotic may have normal lipids, but HDL tends to decrease and LDL tends to increase as kidney function worsens (Farbakhsh & Kasiske, 2005). The observed relationship between abnormal lipid profile and proteinuria is another example of the villain-victim relationship: proteinuria potentiates the dyslipidemia, which can lead to further declines in kidney function and exacerbation of the proteinuria.

A review of data from the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) by Rahman et al. (2003) demonstrated that patients with stage 3 and 4 CKD at baseline had

average total cholesterols of 220 and 227 mg/dL respectively and mean LDL cholesterol of 138 and 143 mg/dL respectively. Despite these laboratory values, only 16% were receiving pharmacologic treatment for their lipid abnormalities. Estimates of the prevalence of dyslipidemia in those with stage 5 CKD from K/DOQI Guidelines for treating dyslipidemias cite LDL levels greater than 100 mg/dL in 56% of patients on hemodialysis, 73% of patients on peritoneal dialysis, and nearly 90% of recipients of kidney transplant (NKF, 2003). Given that CKD is considered to be a cardiovascular disease risk equivalent (Chobanian et al., 2003), total cholesterol and LDL values such as these are not within target ranges. Greater attention needs to be paid to dyslipidemia in the CKD population to improve on these findings. Even though "...patients with CKD undergoing intensive lipid level lowering do not show the same improvement in ischemic or atherosclerotic burden as patients with CAD [coronary artery disease]" (Fathi et al., 2004, p. 51), statin use has been associated with a reduction in cardiovascular related death in patients on dialysis (Seliger et al., 2002).

In contrast, Liu et al. (2004) reported an unexpected finding: there is an inverse association between cholesterol levels and mortality in patients on dialysis. In this prospective study of 823 patients who initiated dialysis, lower total cholesterol was associated with higher total mortality. Measures for malnutrition and inflammation (including serum albumin levels, c-reactive protein, and interleukin 6) were also evaluated. The researchers concluded that the inverse association between cholesterol and mortality in patients on dialysis was more likely due to the effects of systemic inflammation and malnutrition, and not due to some occult protective effect of high cholesterol levels. The authors recommended treatment for dyslipidemias as a way to help lower the CVD risk profile.

Although there is an association among CKD, dyslipidemia and

increased all-cause mortality and CVD risk, a causal relationship has not yet been proven in clinical trials (Sarnak et al., 2003). In this complex patient population, it may be difficult to prove causality, but treatment plans to reduce overall CVD risk profile would seem prudent.

Anemia

Anemia has long been recognized as a complication of CKD. The kidneys are primarily responsible for the production of erythropoietin (EPO), the endogenous hormone that stimulates production of red blood cells (RBCs). EPO stimulates the division and differentiation of progenitor cells within the bone marrow and induces the release of reticulocytes from the marrow into the bloodstream, where they mature into erythrocytes, or mature RBCs. Besides carrying oxygen to tissues, erythrocytes are highly effective scavengers of free radicals, thereby reducing oxidative stress (Siems et al., 2003).

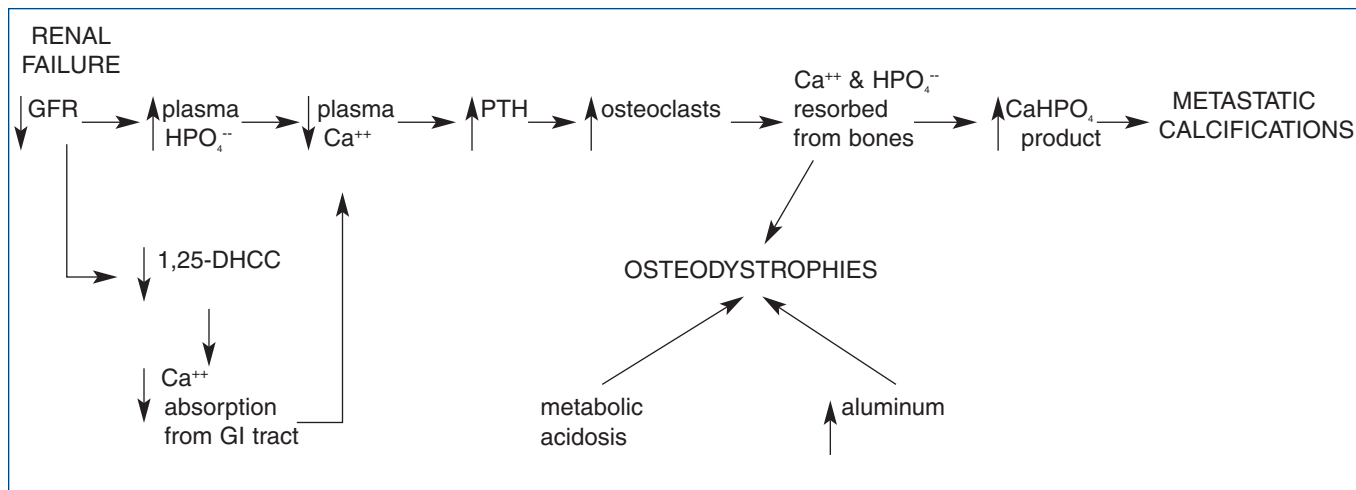
CKD related anemia results from both a decrease in production of EPO from the diseased kidneys and a shortened life span of RBCs in uremia. This can develop early in CKD, with 25% of patients in stage 3 and 50% of patients in stage 4 presenting with anemia (Gomez & Carrera, 2002). Other factors contributing to anemia include blood loss, hemolysis, iron deficiency, and deficiency of either folate or cobalamin (B12). Signs and symptoms of anemia include pallor, fatigue, exercise intolerance, dyspnea on exertion, chest pain, tachycardia, impaired cognitive function, and a loss of a sense of well-being. Symptoms are more likely to present as hemoglobin levels fall below 11 gm/dL.

Anemia is considered one of the primary risk factors for the development of HF, LVH, and left ventricular dilation (London, 2003a) in the patient population with CKD. A reduced red cell mass decreases blood viscosity, decreases peripheral vascular resistance, leading to increased venous return and

increased heart rate and cardiac output (London, 2003b). Oxygen delivery to the myocardium is decreased in the face of this increased demand, with chest pain a possible consequence. Initially, vasodilation leads to increased pre-load and decreased afterload and is a compensatory response, helping to maintain tissue oxygenation (Vlagopoulos & Sarnak, 2005). In the long term, chronic anemia contributes to LVH and cardiomyopathy, with lower hemoglobin levels associated with left ventricular dilation (by echocardiography) and increased incidence of HF as well as increased mortality (Foley et al., 1996). Evidence suggests that "...the combination of anemia and CKD conferred a synergistic risk for stroke and coronary disease compared with each risk factor alone" (Vlagopoulos & Sarnak, 2005).

Treatment for anemia is available and recommended for patients with CKD as soon as anemia is detected. Patients who received erythropoietin stimulating agent (ESA) therapy prior to the initiation of dialysis had improved survival outcomes compared with patients who did not receive this therapy (Fink, Blahut, Reddy, & Light, 2001). There is also evidence that partial correction of anemia in CKD can lead to regression of left ventricular mass (Pendse & Singh, 2005). Treatment of anemia with at least partial correction can be considered an antioxidative therapy contributing to CVD risk reduction (Siems et al., 2003). The most recent K/DOQI guidelines regarding anemia recommend a hemoglobin target between 11 and 13 gm/dL as there is insufficient evidence to recommend hemoglobin levels above 13 gm/dL (NKF, 2006). Berns (2006b) cites preliminary evidence from the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial of adverse outcomes related to correction of anemia to near normal levels (13.5 gm/dL). Various trials have suggested adverse consequences of correcting anemia to normal or near-normal levels, including increased risk of cerebrovascular

Figure 3
Events related to calcium-phosphate imbalances, secondary hyperparathyroidism, osteodystrophies, and metastatic (vascular) calcifications. Adapted from Lancaster (2001) with permission.



events, access thrombosis, and hypertension (Berns, 2006b). To date, the entire relationship between anemia, CKD and CVD risk is not completely understood.

Abnormal Bone Mineral Metabolism

The kidney plays a vital role in the handling of calcium and phosphorus. It also activates vitamin D by hydroxylating 25-hydroxyvitamin D to calcitriol (1,25-dihydroxyvitamin D). Early in CKD, phosphorus levels increase due to reduction in renal clearance; calcium levels typically decrease due to decreased calcitriol with resultant decreased calcium absorption from the gut and decreased calcium release from bone. As CKD progresses, increased demand is placed on the parathyroid gland from low plasma calcium levels and the lack of calcitriol (which normally helps suppress parathyroid hormone (PTH) results in hyperplasia of the gland. Decreased sensitivity of the hypertrophic parathyroid gland to plasma calcium levels may result in an altered ‘set-point;’ that is, a higher level of calcium is generally required to suppress PTH secretion. These alterations can lead to elevations in PTH and ultimately,

the development of secondary hyperparathyroidism (SHPT) that begins early in CKD (Slatopolsky, Brown, & Dusso, 2001). Figure 3 illustrates key components of the abnormalities in bone mineral metabolism associated with CKD. SHPT begins early in CKD. De Boer, Gorodetskaya, Young, Hsu, and Chertow (2002) evaluated 218 patients in an ambulatory nephrology practice, following intact PTH and estimated glomerular filtration rates. They found PTH levels to be inversely related to GFR ($p < 0.0001$) and associated with CVD.

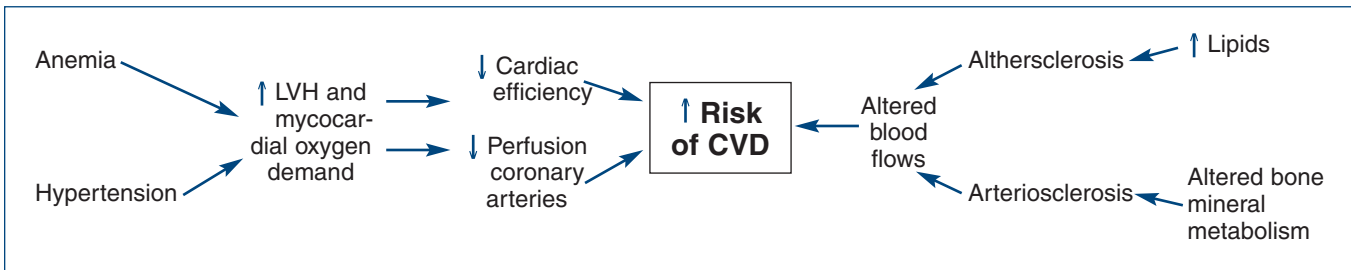
Dietary restriction of phosphorus early in CKD has been found to mitigate development of SHPT (Slatopolsky et al., 2001). Historically, aluminum based phosphorus binders were used to control hyperphosphatemia, but concerns over the toxic effects of aluminum along with the availability of calcium based binders led to a shift in routine treatment (although they may still be used for very short-term rescue therapy). Calcium-based binders were not as potent, however, and large daily doses of calcium are required to manage hyperphosphatemia, creating a positive calcium balance and creating new difficulties associated with hypercalcemia. Amidst the concern over

potential adverse effects of increased calcium load in the form of oral phosphate binders, the National Kidney Foundation K/DOQI guidelines recommend avoidance of calcium salts in patients dependent on dialysis with plasma calcium levels greater than 10.2 mg/dL or in patients with severe vascular or other soft tissue calcifications (NKF, 2003).

Abnormalities in blood levels of calcium, phosphorus, or PTH levels have all been linked to poor outcomes in patients with CKD (Vlagopoulos & Sarnak, 2005). In a national study by Block, Hulbert-Shearon & Levin (1998) using data from the United States Renal Data System (USRDS) on patients on dialysis, hyperphosphatemia was found to result in progression of SHPT and a predisposition for metastatic (extraskelatal) calcification when the calcium/phosphorus product is elevated. The impact on mortality in this analysis is striking. For patients with a serum phosphorus greater than 6.5 mg/dL, the relative risk of mortality was 1.27 compared to patients with phosphorus levels between 2.4-6.5 mg/dL; patients with a calcium phosphorus product greater than 72 mg²/dL² had a 1.34 relative risk of mortality compared to those with a

Figure 4

This figure highlights a few of the postulated pathophysiologic links between CKD and increased CVD risk.



product between 42-52 mg²/dL². Similarly, Kestenbaum et al. (2005) looked retrospectively at 3490 patients with CKD (not requiring dialysis) from the Veterans Affairs' Medical Centers in the Pacific Northwest. They found that serum phosphate levels greater than 3.5 mg/dL were associated with a significantly increased risk for death (all cause mortality). This risk increased linearly with each 0.5 mg/dL increase in phosphorus level.

Excess calcium can be deposited into soft tissue but also into blood vessels, myocardium, and cardiac valves. Vascular calcification is accelerated in patients with CKD (Goodman et al., 2004). Calcium deposited into arteries can be deposited into either the intimal or medial layers. Both intimal and medial calcification are generally co-localized to the coronary, aortic, and ilio-femoral vessels (Afzali & Goldsmith, 2006). Consequences of these two forms of arterial calcification are thought to be fundamentally different (Goodman et al., 2004). The intimal calcification occurs within atherosclerotic plaques, especially in larger, more 'mature' lesions. Since intimal lesions narrow the arterial lumen, blood flow may be compromised with relatively chronic ischemia or even necrosis as the result. Acute ischemic events can also be associated with intimal lesions, as when these plaques rupture and thrombosis occludes the vessel lumen, such as with acute coronary syndrome (Goodman et al., 2004). The CKD population is at particularly high risk, since atherosclerotic

plaques grow more rapidly in the uremic milieu (Amann et al., 2003). Calcification may be present in up to 80% to 90% of atheromatous lesions (Goodman et al., 2004).

Medial lesions (also referred to as Monckeberg's medial sclerosis) contribute to stiffness of the vessels and reduce vascular compliance (Giachelli, 2004). In fact, bone proteins and out-right bone and cartilage formation have been found in calcified vascular lesions, and "...cells derived from the vascular media undergo bone- and cartilage-like phenotypic change and calcification in vitro under various conditions" (Giachelli, 2004, p. 2960). Stiff arteries have a reciprocal relationship with hypertension: that is, medial lesions worsen blood pressure. Systolic BP rises, diastolic pressure remains unchanged or is even lowered, pulse pressure widens, and pulse wave velocity increases (Goodman et al., 2004).

These changes appear to begin before CKD progresses to the point where kidney replacement therapy is required. M. C. Wang, Tsai, Chen, and Huang (2005) found a stepwise increase in arterial stiffness as CKD progressed. In their cross-sectional study of 102 patients with varying stages of CKD, patients with stages 3 and higher CKD had an increase in arterial stiffness, measured as increased pulse wave velocity. That is, the stiffer the vessels, the faster the pulse wave travels along the vessel. This rapidly transmitted forward wave gets reflected back to the central aorta during late systole or early diastole, increasing cardiac afterload, con-

tributing to LVH, and compromising perfusion of the coronary arteries (Giachelli, 2004; Kaplan, 2006).

Reduced vascular compliance due to medial calcification leads to abnormal autonomic and endothelial vasomotor function and a widened pulse pressure (Afzali & Goldsmith, 2006). High systolic pressure increases the workload of the heart with increased myocardial oxygen demand, and a low diastolic pressure can result in decreased perfusion of the coronary arteries, with a net effect predisposing to ischemia (Townsend, 2006). MI, valvular heart disease, congestive heart failure, endocarditis, and death have all been associated with arterial calcification in adults with CKD (Goodman et al., 2004). Further, the fatality rate in patients with uremia post MI is also disproportionately high, with a 1-year post MI mortality of 55.4% and 62.3% in patients with uremia (with and without diabetes mellitus, respectively) compared to 10% - 15% in patients without uremia (Amann et al., 2003). In fact, "...level of renal function seems to be one of the most important factors determining survival after a myocardial infarction" (Pendse & Singh, 2005, p.549).

Braun (1996) found the prevalence of calcification of the aortic and mitral valves to be 55% and 59% respectively in a series of patients on dialysis. Table 3 summarizes some of the risk factors for valvular calcification in CKD and the general population. Although mitral and aortic valve calcification are present, and actually tend to occur at an earlier age in patients with CKD than in individuals

with normal renal function, tricuspid and pulmonic valve calcification is rarely associated with CKD (Cunningham, Corretti, & Henrich, 2006). Valvular calcification in CKD is associated with inflammation, carotid atherosclerosis, and arterial calcification, supporting the hypothesis that valvular calcification is a marker of arterial calcification in patients with advanced CKD (A. Y. Wang et al., 2005).

Summary

While it has long been recognized that patients with end stage renal disease have a tremendous burden of CVD, more and more evidence points to the development of many of these risks in the earlier stages of CKD. Figure 4 illustrates the mechanisms just discussed. This should lead to a focus on ways in which the CVD risk can be minimized, with assessments and interventions for slowing or halting progression of traditional and CKD specific pathology that contribute to CVD. Some suspect chronic inflammation and oxidative stress may prove to be the underlying link between many of the risk factors and the CVD outcomes. Although many questions remain unanswered regarding the links between CKD and CVD, there are numerous known risk factors that can be addressed in an effort to improve patient outcomes. Nephrology nurses in all venues can facilitate this effort. Treatment options for complications will be addressed in the next article in this series.

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Statements of Disclosure

Nephrology Nursing Journal Editorial Board

Patricia B. McCarley, RN, MSN, NP, disclosed that she is on the Consultant Presenter Bureau for Amgen, Genzyme, and OrthoBiotech. She is also on the Advisory Board for Amgen, Genzyme, and Roche and is the recipient of unrestricted educational grants from OrthoBiotech and Roche.

Karen C. Robbins, MS, RN, CNN, disclosed that she is on the Speakers' Bureau for Fallon Medica.

Paula Dutka, MSN, RN, CNN, disclosed that she is a consultant for Hoffman-La Roche and Coordinator of Clinical Trials for Roche.

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Chronic Kidney Disease and Cardiovascular Disease: Pathophysiologic Links

LaVonne Burrows, APRN, BC, CNN

Robert Muller, MSN, RN, FNP-C

Posttest – 1.5 Contact Hours

Posttest Questions

(See posttest instructions on the answer form, on page 65.)

- In patients with evidence of end organ damage, what 10-year sustained reduction in systolic blood pressure (BP) would prevent 1 death in 9 patients treated?**
 - 4 mmHg
 - 8 mmHg
 - 10 mmHg
 - 12 mmHg
- Hypertension leads to kidney damage due to**
 - glomerular cell injury only.
 - glomerular and endothelial cell only.
 - glomerular, endothelial, and mesangial cell only.
 - glomerular, endothelial, mesangial, and epithelial cell injury.
- Which statement is true about sympathetic overactivity in the kidney in patients with CKD?**
 - It leads to decreased catecholamines which contribute to a rise in BP.
 - It is dependent on the activation of the renin-angiotensin-aldosterone system (RAAS).
 - It can be normalized by calcium channel blockade.
 - It can be caused by bilateral nephrectomy.
- Which statement is true about left ventricular hypertrophy (LVH)?**
 - LVH is an adaptive process and can be normal in certain conditions.
 - A decrease in the number of sarcomeres contributes to abnormal systolic function.
 - Concentric LVH refers to increase in volume capacity of the chamber.
 - Eccentric LVH is an increase in wall thickness.
- LVH is a poor prognostic finding with a host of associated adverse effects, including**
 - heart failure only.
 - heart failure and ventricular arrhythmias only.
 - heart failure, ventricular arrhythmias, and myocardial infarction only.
 - heart failure, ventricular arrhythmias, myocardial infarction, and sudden cardiac death.
- As kidney function declines what dyslipidias usually occur?**
 - Decreased total cholesterol
 - Increased HDL
 - Decreased triglycerides
 - Increased LDL
- What were the unexpected findings by Liu et al (2004) concerning higher cholesterol levels in patients on dialysis?**
 - Increased morbidity
 - Decreased mortality
 - Increased HDL
 - Decreased LDL
- Which of the following is a compensatory response in anemia that helps to maintain tissue oxygenations?**
 - Vasodilation leads to increased preload and afterload.
 - Decreased heart rate increases cardiac output.
 - Decreased peripheral vascular resistance leads to increased venous return.
 - Decreased red cell mass leads to increased viscosity.
- In a study by Kestenbaum and colleagues of 3490 patients not on dialysis, the relative risk of death was associated with phosphate levels greater than**
 - 3.5 mg/dl.
 - 4.0 mg/dl.
 - 4.5 mg/dl.
 - 5.0 mg/dl.
- Arterial medial calcification is associated with**
 - higher systolic BP only.
 - higher systolic BP and lower diastolic BP only.
 - higher systolic BP, lower diastolic BP, and widening of the pulse pressure only.
 - higher systolic BP, lower diastolic BP, widening of the pulse pressure, and decrease in the pulse wave velocity.

ANNJ704

ANSWER/EVALUATION FORM

Chronic Kidney Disease and Cardiovascular Disease: Pathophysiologic Links

LaVonne Burrows, APRN, BC, CNN and Robert Muller, MSN, RN, FNP-C

Posttest Instructions

- Select the best answer and circle the appropriate letter on the answer grid below.
- Complete the evaluation.
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|------------|------------|------------|------------|-------------|
| 1. a b c d | 3. a b c d | 5. a b c d | 7. a b c d | 9. a b c d |
| 2. a b c d | 4. a b c d | 6. a b c d | 8. a b c d | 10. a b c d |

Evaluation	Strongly disagree		Strongly agree		
	1	2	3	4	5
1. The objectives were related to the goal.	1	2	3	4	5
2. Objectives were met					
a. Describe the villain-victim development of hypertension in patients with CKD.	1	2	3	4	5
b. Identify dyslipidemias seen in patients with CKD.	1	2	3	4	5
c. Discuss anemia and its contribution to development of left ventricular hypertrophy (LVH).	1	2	3	4	5
d. Describe the development of arterial stiffness in patients with CKD.	1	2	3	4	5
3. The content was current and relevant.	1	2	3	4	5
4. This was an effective method to learn this content.	1	2	3	4	5
5. Time required to complete reading assignment: _____ minutes.					

GOAL

Identify pathophysiologic mechanisms by which risk factors for cardiovascular disease contribute to the increased cardiovascular morbidity and mortality seen in individuals with chronic kidney disease (CKD).

I verify that I have completed this activity:

(Signature)

Comments _____

Suggested topics for future articles? _____