CHRONIC KIDNEY DISEASE: A MARKER OF CARDIOVASCULAR DISEASE

Juan Jorge Olivero, M.D.; Peter Tuan Nguyen, M.D.; Juan Jose Olivero, M.D.
Methodist DeBakey Heart & Vascular Center, Houston, Texas

Background

Chronic kidney disease (CKD) affects approximately 20 million Americans. As a result, it is essential for non-nephrology physicians to actively participate in the early detection of this problem.[1] Because the kidneys are highly vascular organs, the finding of microalbuminuria is now accepted as an early marker of systemic cardiovascular disease (CVD).[2] In fact, there is evidence that improving microalbuminuria results in improved cardiovascular and renal outcomes.[3] Hypertension, anemia, hyperlipidemia, inflammation, secondary hyperparathyroidism with calcium-phosphorus metabolic abnormalities, and hyperuricemia are present in CKD patients — all risk factors leading to CVD.[4] A systematic diagnostic and therapeutic approach is needed to correct these risk factors and prevent progression of both CKD and CVD.

The National Kidney Foundation published a new classification of CKD based on glomerular filtration rate (GFR) (Table 1).

The Modification of Diet in Renal Disease (MDRD) formula to estimate GFR takes into account age, gender, race, BUN, creatinine and albumin, all important contributing factors in determining kidney function. This formula, which can be found on www.mdrd.com, is widely used as an estimate of kidney function. Many laboratories now report eGFR based on this equation. Since the American population is aging, this formula is important when considering medication dosing or diagnostic procedures. Identifying patients at CKD stage 3 and above results in increased attention to a population at risk of progression to stage 5 kidney failure, cardiovascular disease and death. Targeted eGFR screening to high-risk individuals (diabetics, hypertensives, family history of kidney disease, smokers or those with micro or macroalbuminuria) instead of universal screening is probably the most appropriate thing to do. However, key factors such as age and gender may result in an expected decrease in GFR, and labeling this expected drop as "disease" could affect insurability, employability and the capability to become organ donors. It has been estimated that there is an age-related expected decline in kidney function of approximately 10 mL/min per decade after the age of 40, which may not be reflected

Table 1. Classification of CKD based on glomerular filtration rate.

STAGE	DESCRIPTION	GFR (mL/min/1.73 m²)
1	Kidney damage with normal or increased GFR	>90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure (dialysis or transplantation)	<15

Figure 1. Prevalence of patients with chronic kidney disease.[39]

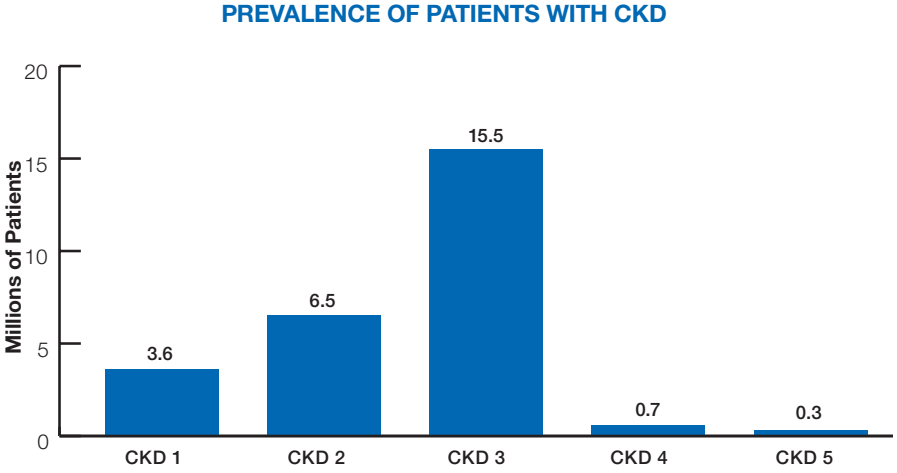


Table 2. Factors known to alter BUN/creatinine ratio.

FACTORS KNOWN TO ALTER BUN/CREATININE RATIO	
↑ ↑ BUN ↑ CREATININE	↑ BUN ↑ ↑ CREATININE
Volume depletion	Rhabdomyolysis
Drugs (corticosteroids, tetracycline)	Decreased protein intake
Obstruction	Liver failure
Hypercatabolic state (sepsis)	Increased muscle mass
Tissue necrosis (gangrene, burns)	Ketosis
Gastrointestinal bleeding	Drugs (cimetidine, cefoxitin trimethoprim-sulfamethoxazole)
Reduced muscle mass	
Increased protein intake	
Urine extravasation in peritoneum	

in the serum creatinine level. Other situations known to affect BUN and creatinine levels and alter the expected 10:1 BUN/creatinine ratio are summarized in Table 2.

Microalbuminuria: The Cardiorenal Connection

There is ample evidence in the renal literature that microalbuminuria (microalbumin levels >30 mg/gm creatinine) is a simple marker of an atherogenic milieu. Although the exact pathophysiologic mechanism linking CKD with CVD has not been fully elucidated, it has been proposed that microalbuminuria reflects subclinical vascular damage (endothelial dysfunction) in the kidneys and other vascular beds. Independent of traditional risk factors, prospective epidemiologic studies have found microalbuminuria to be a risk factor of all-cause CVD and mortality, more predictable among diabetics but also among nondiabetic hypertensive individuals and the general population.[5-9] The association of kidney dysfunction and albuminuria with cardiovascular mortality is more evident among older rather than younger individuals.[10]

There is significant evidence that treatment of microalbuminuria with angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin receptor blockers (ARBs) reduces cardiovascular risk.[8,9] The initial studies using ARBs to reduce albuminuria in type 2 diabetes mellitus have been subsequently extrapolated for the treatment of microalbuminuria of any etiology. It has also been shown that combination therapy of ACEIs plus ARBs has a synergistic effect, reducing proteinuria levels more than if either of those drugs were used alone.[11] Lately, the combination of an aldosterone receptor blocker (e.g., spironolactone) and ACE-I[12] but not the combination of ACE-I, ARB and spironolactone1[3] has also shown a beneficial effect in decreasing albuminuria, thus preventing cardiovascular events and progression of CKD. The newest rennin inhibitor, aliskiren, in combination with ARB has also been reported to have a beneficial effect in reducing proteinuria.[14] The combinations mentioned above could result in hyperkalemia, particularly in patients with stage 3 or 4 CKD; stage 5 CKD contraindicates this approach. If hyperkalemia becomes a limiting factor, the addition of hydrochlorothiazide (HCTZ) or loop diuretics, particularly if edema is present, could mitigate the problem.

For blood pressure control, the addition of ARB to ACEIs is of no major impact in achieving normotension. In this case, either HCTZ and/or a calcium channel blocker (CCB), such as amlodipine, should be the next drugs of choice. Of note is the fact that the simultaneous use of ACE-I, ARB, and beta-blockers has been associated with increased cardiovascular mortality.[15] In summary, as part of the annual screening, physicians should measure urinary microalbumin, lipids, and other routine metabolic profiles. In addition, therapy with the programs outlined above should be initiated to prevent progression of CKD and CVD.

Anemia of CKD and the Heart

Anemia usually becomes apparent when GFR is less than 50 mL/min. Provided that other etiologies, such as chronic blood loss, iron deficiency, vitamin B12 or folate deficiency, and myelodysplastic syndromes, have been ruled out; this finding is mostly due to decreased erythropoietin synthesis, leading to diminished bone marrow red cell production. Progressive left ventricular dilatation (LVD) with progressive death of myocytes, evolving into cardiomyopathy and heart failure, as well as asymptomatic ischemic heart disease, is responsible for the high mortality of CKD patients. The combination of

anemia, hypertension, and volume overload has been directly correlated with those complications and usually leads to high output failure.[16] Treatment of anemia with erythropoietin or darbepoietin improves angina and heart failure symptoms and partially ameliorates left ventricular dilatation and hypertrophy, with improvement of both morbidity and mortality.[17] Likewise, by improving hemoglobin levels, there is better oxygen-hemoglobin carrying capacity to the renal interstitium, thus preventing or slowing down progression of CKD. Erythropoietin is also an important source of production of bone marrow-derived endothelial progenitor cells. These cells gain access to the circulation and are important contributors of angiogenesis and maintenance of vascular integrity.[18] However, recent data cautions about the over-correction of anemia since it has increased the incidence of vascular thrombotic occlusive events, in turn leading to increased cardio- vascular mortality.[19] The newer recommendations advise to maintain hemoglobin levels around 11 gm/dL.

CKD-Inflammation and Accelerated Atherogenesis

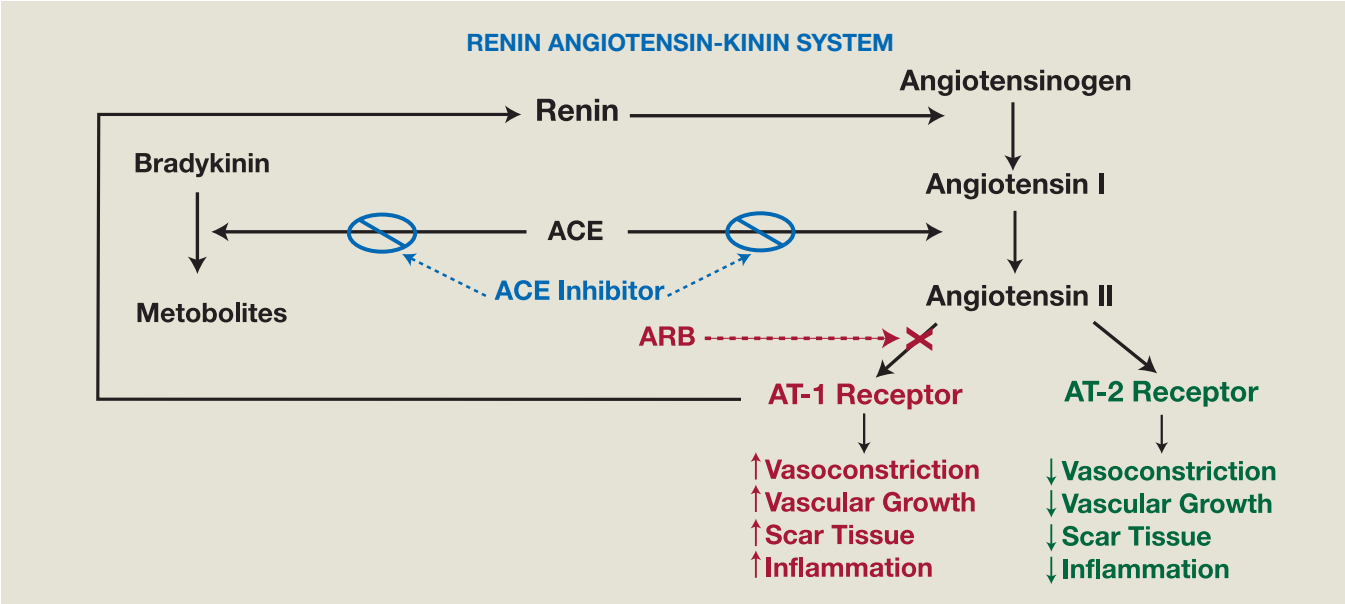
Endothelial dysfunction, a pro-atherogenic alteration, is present even in the early phases of CKD and manifested by elevated C-reactive protein levels. The inflammatory state in these patients is due to several factors, including diminished clearance of pro-inflammatory cytokines, accumulation of low-density lipoproteins, and increased advanced glycosylation end products as well as lipoprotein (a). This, along with accumulation of the endogenous inhibitor of nitric oxide (NO) synthase and asymmetric dimethylarginine (ADMA), results in oxidative stress, sodium retention, and hypertension. ADMA levels are associated with cardiovascular risk in the general population,[20] and ADMA accumulation and NO inhibition may accelerate progression of CKD.[21] Moreover, ADMA appears to be a mediator of the atherogenic effects of increased sympathetic activity.[22] Another important adverse effect of inflammatory cells (monocytes, macrophages) is potentiating alkaline phosphatase activity of osteoclast-like cells in the vascular system, resulting in vascular calcification.

Other than the use of statins, specific therapeutic interventions have not become standardized to offset these complications except for general measures such as discontinuation of smoking, maintaining a healthy diet, and exercising.

Hypertension: Cardiorenal Effects

Left ventricular hypertrophy (LVH) is the most common complication found in CKD patients and results from sympathetic system hyperactivity leading to increased vascular resistance and chronic volume overload. Hypertension leads to concentric LVH, whereas the combination of hypervolemia, anemia, and hyperdynamic circulation results in increased cardiac output and development of eccentric LVH. In general, LVH begins as an adaptive mechanism to accommodate pressure secondary to volume overload. However, as time progresses, it becomes a maladap-

Figure 2. Renin angiotensin-kinin system.



tive phenomenon leading to diastolic dysfunction.[23] Prospective studies have shown decreased LV width using ACEIs and lately also with ARBs.[24] Since LVH has been associated with sudden death, these agents should be the preferred drugs of choice, often in combination with HCTZ. Sodium restriction (2 gm/day) and total fluid restriction <1,500 mL/day should be strongly recommended since drinking large amounts of fluid while simultaneously receiving diuretics not only is contradictory but can also lead to hyponatremic encephalopathy.[25] Although comparative long-term studies between ACEIs and ARBs are not available, it appears that the use of ARBs is more advantageous than ACEIs — not only because of the decreased incidence of angioneurotic edema but also because of their mechanism of action, whereby ARBs selectively block AT-1 receptors and leave the "beneficial" effects of the renin angiotensin system of the AT-2 receptors unabated (Figure 2).

Provided hyperkalemia does not become a limiting factor, aldosterone receptor blockade with spironolactone (less expensive) at a small dose of 25 mg/day, or eplerenone at 50 mg/day (if intolerant to spironolactone or if problems with gynecomastia occur), should be added to ARB/HCTZ combination since the use of the former has also been shown to improve cardiac outcomes[26] and slow down progression of kidney disease.[27]

Cardiac Effects of Hyperlipidemia in CKD

Patients with CKD tend to have a different lipoprotein pattern compared to the general population. Hypertriglyceridemia is more common in patients with CKD, and this is an important contributor to CVD. The cardiovascular risk of triglycerides may be the result of atherogenic "remnant lipoproteins" composed primarily of VLDL cholesterol. This moiety is not routinely reported, but it can be estimated by subtracting HDL from total cholesterol.[28] Intermediate-density lipoprotein (IDL) cholesterol is another remnant lipoprotein included in the non-HDL cholesterol fraction that also has important atherogenic effects. Serum IDL levels reportedly are higher in patients with CKD. Statins reduce IDL, and although there is no data indicating reduction in cardiovascular mortality, some have suggested that IDL cholesterol may be an important lipid component to target in patients with CKD.[29] Lipoprotein (a), a modified form of LDL, is a highly atherogenic lipoprotein particle that appears to be important in the pathogenesis of CVD in the CKD population. This particle binds to macrophages and promotes foam cell formation and deposition of cholesterol in atherosclerotic plaques.[30] Statins are the standard of care since, in addition to their lipid-lowering effect, they have anti-oxidant properties and anti-inflammatory effects, thus ameliorating the atherosclerotic process.[31]

Cardiovascular Effects of Parathyroid Hormone Excess in CKD

Vascular calcification is a frequent feature in CKD patients and contributes to cardiovascular mortality. Hyperphosphatemia occurs as a consequence of decreased renal excretion in CKD and is responsible for the development of secondary hyperparathyroidism, which in turn leads to osteodystrophy with calcific arteriopathy and valvulopathy.[32] Under a "uremic milieu" and the presence of hyperphosphatemia, vascular smooth muscle cells increase production of osteopontin with ensuing vascular calcification.[33] In fact, in about 15% of human atheromatous plaques, the calcium deposits undergo changes of complete bone architecture that are histologically indistinguishable from trabecular bone, including even marrow and cartilage.[34] Elevated calcium x phosphorus product (>50 mg/dL) along with secondary hyperparathyroidism has been associated with increased cardiovascular mortality in the majority of CKD patients.[35] As a result, the consensus of opinion is to normalize these parameters to prevent cardiovascular complications. Consequently, a low phosphorus diet (<900 mg/day) with avoidance of exogenous calcium intake (even in the form of phosphate binders) as well as aggressive control of hyperphosphatemia (phosphorus levels >5 mg/dL) is very important. Likewise, suppression of parathyroid hormone excess by hormone D-1,25$(OH)_2$ cholecalcipherol or, in case of coexistent hypercalcemia, with calcimimetics (cinecalcet) is also extremely important. In severe cases of hyperparathyroidism unresponsive to the above-mentioned approach, total parathyroidectomy and subsequent parathyroid tissue implantation in the forearm is the conduct to follow. In fact, there are observational studies suggesting that the latter approach reduced long-term mortality among dialysis patients by 15%.[36]

Uric Acid: Cardiorenal Connection

Hyperuricemia (uric acid >8 mg/dL) is now considered an independent risk factor for progressive vascular injury that can lead to hypertension, loss of kidney function, and increased cardiovascular morbidity and mortality.[37] Uric acid

leads to endothelial dysfunction, vascular proliferation, and nitric oxide release from endovascular cells.[38] Discontinuation of diuretics when appropriate and initiation of allopurinol to correct hyperuricemia is important in the prevention of the above mentioned complications.

Summary

The risk of developing CVD is high among CKD patients and, as a result, cardiovascular-related complications account for high morbidity and mortality. Multiple factors contribute to CVD in CKD patients, including hypertension, anemia, inflammation, hyperlipidemia, calcium-phosphorus-parathyroid hormone imbalance, and hyperuricemia. Each one of these complications needs to be identified and treated in an attempt to improve survival. Early markers of CVD such as microalbuminuria and uric acid levels need to be added to the routine annual evaluation, particularly among high-risk individuals such as diabetics, hypertensives, smokers, and the elderly. Likewise, the use of eGFR is highly recommended as a screening tool in those individuals.

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