*Review Article*

# Renal-Cerebral Pathophysiology: The Interplay Between Chronic Kidney Disease and Cerebrovascular Disease

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*Objectives:* Cerebrovascular disease has increasingly been linked to overall vascular health. Pathologic conditions like diabetes, hypertension, and kidney disease have been shown to affect brain health and cerebrovascular and nervous systems. Acute kidney injury (AKI) and chronic Kidney Disease (CKD) represent a variety of vascular insults that can adversely affect cerebral health. Hypertension, fluctuations in blood pressure, and diabetic vasculopathy are known risk factors for cerebrovascular disease associated with CKD. Other emerging areas of interest include endothelial dysfunction, vascular calcification due to calcium and phosphorus metabolism dysregulation, and uremic neuropathy present the next frontier of investigation in CKD and cerebrovascular health. *Methods:* It has become apparent that the interrelation of AKI and CKD with vascular health, chemical homeostasis, and hormonal regulation upset many aspects of cerebral health and functioning. Stroke is an obvious connection, with CKD patients demonstrating a higher proclivity for cerebrovascular accidents. Cerebral bleeding risk, uremic neuropathies, sodium dysregulation with impacts on nervous system, vascular calcification, and endothelial dysfunction are the next salient areas of research that are likely to reveal key breakthroughs in renal-cerebral pathophysiology. *Results:* In this review nephrological definition are discussed in a neuro-centric manner, and the areas of key overlap between CKD and cerebrovascular pathology are discussed. The multifaceted effects of renal function on the health of the brain are also examined. *Conclusion:* This review article aims to create the background for ongoing and future neurological-nephrological collaboration on understanding the special challenges in caring for patients with cerebrovascular disease who also have CKD.

**Key Words:** Cerebrovascular disease—Chronic kidney disease—Hypertension—Vascular health—Cognitive decline



## Introduction

The role of the kidneys in maintaining chemical homeostasis is a crucial one, and yet it is only one facet of kidney function. The kidneys are involved in continual hormonal communication regulating blood pressure via the renin angiotensin aldosterone system. Other roles include regulation of erythropoiesis, bone mineral composition/calcium homeostasis, sensing of oxygen delivery, and increasingly the kidneys are recognized to be an important center of endothelial signaling.[1]

The brain, like the kidneys is the recipient of a large percentage of cardiac output, and is one of the most sensitive organs, requiring tight specifications to maintain optimal

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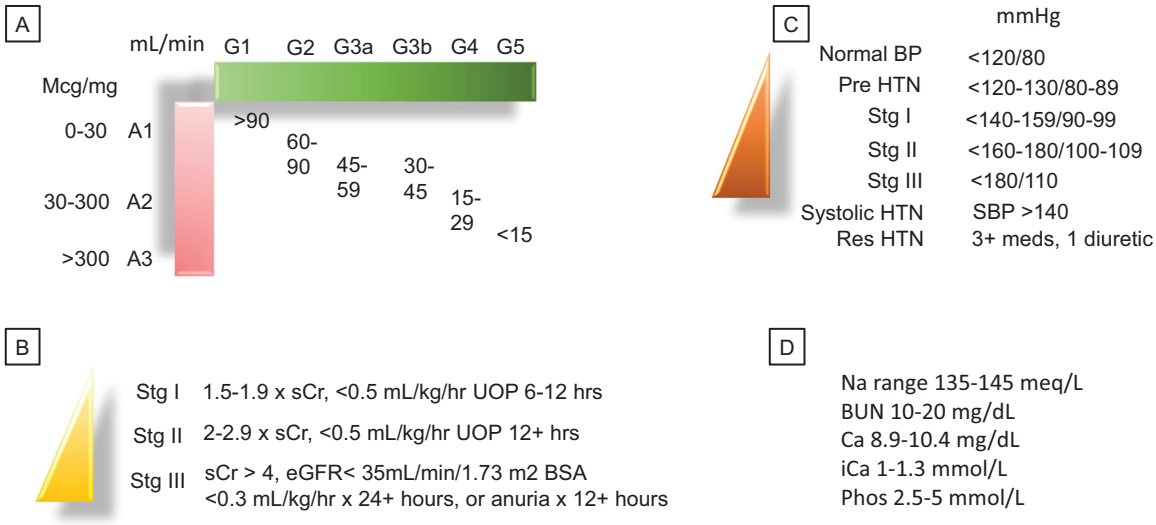


**Fig. 1.** *Basic nephrology guidelines useful for the neurologist. A) Glomerular Filtration (G 1-6), and Proteinuria (A 1-3) KDIGO staging of CKD. B) AKIN Criteria for stage 1-3 AKI. C) JNC- 8 guidelines on hypertension classification. D) Normal range of electrolyte levels Na, sodium; Phos, phosphorous. Legend: A1, stage 1 proteinuria; A2, stage 2 proteinuria; A3, stage 3 proteinuria; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; BP; blood pressure; BSA; body surface area; BUN, blood urea nitrogen; Ca, calcium; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; G1, stage 1 CKD by eGFR; G2, stage 2 CKD by eGFR; G1, stage 3 CKD by eGFR; G1, stage 4 CKD by eGFR; G1, stage 5 CKD by eGFR; G1; h, hours; HTN, hypertension; iCal ionized, calcium; mcg/mg, microgram/milligram; JNC, Joint National Commission; KDIGO, Kidney Disease Improving Global Outcomes; m2, meters squared; meq/L, milliequivalents/Liter; mg/dL, milligrams/deciliter; mL/min; milliters/min; mL/kg/h, milliter/kilogram/h; mmol/L, millimole/L; Na, sodium; Phos, phosphorous; Res, resistant; SBP, systolic blood pressure; sCr, serum creatinine; Stg I, stage I JNC-8 hypertension; Stg II, stage II JNC-8 hypertension; Stg III, stage III JNC-8 hypertension; UOP, urine output.*

function.[2] The delicate neurons are sensitive to perturbations in sodium flux, calcium flux, blood pressure changes, oxygen delivery, and overall cleanliness of the blood from urea associated nitrogenous wastes.[3]

Hence, it is reasonable that the health of the delicate cerebral organ, and the plethora of electrically interconnected and fragile neurons would depend heavily on appropriate renal function.[1] The traditional risk factors of neurological disease associated with the kidneys include acute hypertensive emergencies leading to cerebrovascular hemorrhage, thrombosis from vascular disease leading to infarction, and cardiac disease leading to embolism.[4] Uremic neuropathies, vascular calcification, hyponatremia are also less recognize renal risk factors for neurological disease. Renal failure also contributes to cerebral pathology via increased bleeding risk, phosphatonin level changes, and derangements in calcium and vitamin D homeostasis.[1,5]

All these factors could represent nontraditional risk factors for cerebral disease directly stemming from Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD).[1,5] In this review, presentation of "basic renal definitions" of hypertension, CKD GFR staging, proteinuria staging, role of AKI, proteinuria staging, urinary markers of injury, CKD epidemiology, electrolyte management, and management of CKD comorbidities are also reviewed. The classic risk factors for cerebrovascular disease in CKD are also reviewed, followed by "nontraditional causes of cerebral disease in CKD." It is hoped that closer neurological and nephrological collaboration will yield fruitful discoveries to understand the excess risk of neurological dysfunction in CKD patients.

## Nephrology for neurologists

Hypertension staging at this point is guided by the agreed upon Joint National Comission-8 (JNC-8) on Hypertension control. Normal blood pressure is defined as <120/80 mmHg. Prehypertension is 120-139 mmHg/80-89mmHg. Stage I Hypertension is 140-159 mmHg/90-99 mmHg. Stage II is defined as >160-180/100-110 mmHg of blood pressure. Stage III is defined as >180mmHg/110 mmHg. Isolated systolic hypertension is defined as >140 mmHg systolic reading with a normal diastolic reading. Resistant hypertension is defined as blood pressure uncontrolled despite 3 agents including a diuretic.[6] See Fig. 1.

CKD is defined persistent renal dysfunction, defined as being present for a period of 3 months by the Kidney Disease Advancing Global Outcomes organization (KDIGO). KDIGO is an initiative of the International Society of Nephrology, and presents the most venerable recommendations to improve care of renal worldwide.[7] The staging of chronic kidney disease is defined by two axes, glomerular filtration stage (labeled as G) and proteinuria stage (labeled as A). Glomerular Filtration stage I CKD is the defined as an estimated glomerular filtration rate (eGFR) of <90mL/min with anatomic or other derangements in renal health (proteinuria for example). Stage II is mild

CKD, defined as an estimated glomerular filtration rate of 60-90 mL/min. Stage III is the largest category and defined as moderate CKD, defined as an estimated glomerular filtration rate of 30-60mL/min. Two substages exist, stage IIIa representing eGFR of 45mL/min-60mL/min, and stage IIIb having an eGFR of 30mL/min-45mL/min. Stage IV represents severe CKD with an eGFR of 15-30 mL/min. Stage V represents a failing kidney with a definition of eGFR<15 mL/min. End Stage Renal Disease (ESRD) represents a requirement for renal replacement therapy regardless of underlying eGFR.[7] See Fig. 1.

Proteinuria is the other axis of the KDIGO scoring system and this is similarly staged by degree of albuminuria[7]. It is important to note that albuminuria and total protein/creatinine ratio may not be identical, but are generally within same order of magnitude,[8] except in cases involving globulinemia due to plasma cell dyscrasias. A1 is defined as normal albuminuria with a measurement of <30 mcg/mg (or mg/g) of albumin in urine, which is considered normal. A2 is microalbuminuria or 30-300 mcg/mg of albuminuria. A3 is defined as >300mcg/mg of albumin in the urine and patients who are heavily nephrotic (including those with diabetic nephropathy and glomerular disease typically-but not always-fall in the AIII category.[7] Renal function tends to rapidly worsen in patients with AIII level proteinuria. New criteria in CKD classification also recommend discussing the cause of CKD [C], in addition to the glomerular filtration [G], and albuminuria [A], axes.[3] See Fig. 1.

The most common estimates of eGFR utilize the Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas.[9] Serum Cystatin C level can also be used to estimate eGFR, either alone or in combination with creatinine,[10] since creatinine is also a surrogate of muscle mass and likely also red meat intake.[11] These formulae provide an estimation of the GFR, usually indexed for body surface are, but they are only approximate, and hence are referred to as estimated GFR, i.e., eGFR.[12] Gold standard methods for estimating renal clearance (such as Inulin clearance) and radio-isotope measurements are infrequently used clinically.[13] 24-h collections of urea, creatinine, and new markers like cystatin C can provide a more exact estimate than just serum creatinine.[14] eGFR is still a more useful marker than serum creatinine, since it reflects expected changes in renal clearance due to gender, weight, height, and most importantly age.[15] Currently the CKD-EPI equation is thought to be the most accurate of the 3 models of eGFR estimation. Cystatin C is a new tool for use in serum detection, urine detection (as a marker of renal injury), or as a 24-h urine collection to estimate eGFR via cystatin C clearance calculations.[16] It is actually less biased than creatinine in older patients and patients with liver disease and allows a more accurate eGFR estimate in selected populations.[16] New equations utilizing creatinine and cystatin C have also been shown to be more accurate.[15,16]

AKI is recognized as a short-term impairment of renal function as measured by serum metabolite levels, and urine output. The grading of AKI according to KDIGO is based on prior RIFLE (Risk, Injury, Failure, Loss, ESRD) model, with a closer similarity to the Acute Kidney Injury Network (AKIN) criteria.[17] The KDIGO AKI staging model states stage I AKI is an increase of sCr to 1.5-1.9 x of baseline, or <0.5mL/kg/h of urine output for 6-12 h. Stage II AKI is 2-2.9x increase of sCr above baseline or <0.5mL/Kg/h of urine output for 12 h or more. Stage III AKI represents a sCr of 4mg/dL or initiation of renal replacement therapy, or decrease in eGFR <35 mL/min/1.73 $m^2$ of body surface area. Urinary data suggests stage III AKI by <0.3mL/kg/h of urine output (oliguria) for 24 or more hours or anuria for 12 or more hours.[18]

Urinary Cystatin C, Neutrophil Gelatinase Associated Lipocalin (NGAL), and Kidney Injury Molecule-1 (KIM) are new urinary markers that are also recently being adapted for clinical use to predict AKI more quickly than is possible based on serum creatinine markers and urine output criteria.[19,20] See Fig. 1. One important caveat is that cystatin C can be affected by changes in thyroid function, inflammation, steroid use, active Human Immunodeficiency Virus (HIV) infection, and malignancy.[19] New proposals suggest combining equations utilizing creatinine and cystatin C for optimal accuracy.[21]

## CKD epidemiology

Proteinuria is a major predictor of CKD progression, and most of the patients who progress to ESRD have conditions associated with significant proteinuria.[22] Importantly it is associated with severe vascular inflammation and a prothrombotic state.[23] Macro-angiopathies are frequently seen in proteinuric diabetics, and include coronary artery disease (CAD), peripheral vascular disease (PVD), and cerebrovascular disease (CVD).[24] Micro-angiopathies associated with proteinuria and particular due to diabetic nephropathy include the triad of neuropathy, retinopathy, and nephropathy.[25] Diabetes results in microalbuminuria fairly frequently after 10-15 years of DM2, with shorter duration in patients with uncontrolled disease.[26,27] And proteinuria is strongly linked with worsening eGFR and progression of underlying diabetic nephropathy.[23] Glomerular diseases represent another cause of proteinuria that can result in similar diminution of renal function.[28]

The majority of diabetic patients who progress to ESRD have high grade proteinuria- a statistic that highlights the rapid deterioration of kidney function that can be seen due to nephrotic syndrome.[29] Approximately 50% of patients progressing to ESRD having diabetes, and 12% having another proteinuric glomerular disease.[30] Limited tools exist in the fight against diabetic nephropathy in

particular, and the development of the Sodium-Glucose-Cotransporter-2 (SGLT2) inhibitors is a hopeful development in slowing down the progression of diabetic nephropathy and cardiovascular disease.[31,32]

Progression from CKD to ESRD does not occur in the majority of CKD patients, rather most CKD patients die before they can be started on dialysis.[33] This is because CKD, particularly proteinuric CKD, is a powerful risk factor for cardiac and cerebrovascular events.[34] These events have a high mortality rate.[34]

Pressingly, it is also important that CKD worsens outcomes in patients with diabetes and the metabolic syndrome.[35] Tools to detect and prevent the development and progression of CKD thus, would be predicted to have a strong effect on reducing overall morbidity and mortality in the population of patients with metabolic syndrome.[36] This is supported with data showing a clearly trend to rising rates of hospitalization correlating to more advanced CKD stage 1-6.[37] It is important to also note that the risk of cardiac death in CKD accounts for nearly 42% of deaths, as compared to 31% in the general population.[38] Meaning that cardiac and cerebrovascular events are important contributors to the overall mortality rate in the CKD population.[37]

The numbers seen amongst US patients requiring dialysis are striking, nearly 500,000 patients are currently on dialysis, and 726,000 patients if patients who receive a kidney transplant after being on dialysis are included.[39] Nearly 15% of the US population has CKD.[39] It is for this reason that screening using existing renal disease detection tools is recommended in the general population. We believe CKD should be screened for as aggressively by current US primary care physicians as they screen for hyperlipidemia.

While unfortunately the majority of CKD is progressive and given enough time can lead to ESRD, the rate of progression can be greatly slowed down with attention to blood pressure, medication management, control of risk factors such as Diabetes or other risk factors of glomerular hyperfiltration,[40] and diet (low animal protein diet-LPD).[42,43] The use of Angiotensin Converting Enzyme Inhibitors (ACEi), and other agents to modify the renin angiotensin aldosterone system (RAAS), are one such tool.[44] Other tools being studied are the use of SGLT2 inhibitors in patients with DM2,[32] and use of aldosterone blockade in proteinuric disease, dialysis populations, and in resistant hypertension.[45]

Dietary therapy is increasingly recognized as an opportunity to naturally slow down the progression of CKD. Low animal protein (LPD 0.6-0.8 mg/kg),[42] low salt diets are an example where natural management is expected to be effective at disrupting pathophysiological processes disrupting the integrity of the glomerulus.[42] The reason for this is amino acids result in increased GFR and renal blood flow resulting in a rise of intraglomerular pressure.[46] Several studies demonstrate that low protein diet has a positive effect on renal health, especially a low animal protein diet.[47] Very low protein diets (VLPD 0.4-0.6 g/kg) are expected to have a positive renal effect, but also can come with a risk of malnutrition if not expertly managed.[42] Additional kidney health benefits can be attained from plant-dominant diets, i.e. meal plans with >50% plant source of the protein component.[48]

## Pertinent electrolytes in neurological care

For the purposes of neurological care, sodium levels are defined in the normal range as >135 meq/L, with an absolute maximum correction of 10 meq/L/day.[49] Sodium control remains extremely relevant in neurology given the risk of seizures, cognitive difficulties, gait difficulties, and decreased levels of mentation that are associated with both hyponatremia and hypernatremia.[49] The main risk of acute hyponatremia is due to the development of cerebral edema due to the imbalance of central nervous system and peripheral osmolality.[50] This is the mechanism for the aforementioned perturbations of mentation, gait, memory, and the mediator of more serious risks like seizures.[50] Chronic hyponatremia tends to be less symptomatic, but given physiologic adaptations due to the loss of organic osmoles, rapid correction remains risky to neuron function.[50] Over correction may risk development of osmotic demyelination syndrome (ODS)-a fearsome complication.[51]

Blood urea nitrogen is also associated with nitrogenous wastes thought to cause cerebral dysfunction.[52] Abnormal levels are defined as >20mg/dL. Uremia is defined as at point when symptoms occur, typically >100mg/dL levels of BUN and certainly at greater than 120-150mg/dL at which range seizures can occur.[53] The true toxins that cause encephalopathy rise with an increase in BUN, but are not necessarily the urea itself.[53]

Calcium is defined as abnormal if at or greater than 10.4 mg/dL, or if ionized Ca >1.3 mmol/L.[54] Phosphorous levels can rise due to decreased clearance and in spite of increased levels of phosphatonins, such as Fibroblast growth factor 23 (FGF-23).[55] While these phosphatonins initially clear phosphorous from the circulation, at high levels they become mediators of vascular calcification and inflammation.[55] These are the most pertinent levels of electrolytes involved in the cross talk between nephrology and neurology.

## Management of CKD comorbid disorders

The classic comorbidities of CKD include anemia of CKD, infection risk, electrolyte derangement, metabolic acidosis, bone mineral disease, hypertension, decreased medication clearance.[56] Another crucial possible complication is malnutrition due to protein energy wasting (PEW) in advanced CKD.[42] Many of these effects become more pronounced after CKD stage IIIb (eGFR <45 mL/

min), as this in particular is when phosphorous levels rise and phosphatonin secretion (FGF-23) increases sharply.[56]

Anemia is usually ameliorated with erythropoietin stimulating agents and iron supplementation.[57] Secondary hyperparathyroidism (bone mineral disease) is usually treated with 25 hydroxy vitamin supplementations in mild CKD, and 1,25 dihydroxy vitamin D supplementation in more severe CKD.[58] This is due to the loss of 1 alpha hydroxylase with decreased kidney mass. Vitamin D receptor agonists that are more potent that 1,25 dihydroxy vitamin D are also used in advanced CKD as well as in ESRD.[58]

Malnutrition remains a difficult problem due to the need to decrease protein intake in CKD, while the need in ESRD is to greatly increase protein intake to prevent protein calorie malnutrition.[42] This is likely due to the worsening scope of PEW as CKD advanced into ESRD.[42]

## Traditional mediators of cerebrovascular disease in CKD patients

Traditional mediators refer to well-known mediators of hemorrhagic and atherosclerotic cerebrovascular disease. These include hypertension and atherosclerosis related to hypercholesterolemia respectively. Cerebral changes can also occur because of microbleeds, microinfarcts, white matter lobal atrophy, arteriosclerosis.[1] Given the delicate nature of neural circuits the accumulation of white matter, neuronal, and vascular disease explains the cerebral changes seen in CKD/ESRD patients.[1] Since cerebrovascular disease often involves small vessel disease (SVD), the associated symptoms of cognitive impairment may become clinically apparent only after some time.[5] Given the geographical coding of cerebral tissue, different manifestations may occur depending on where the SVD occurs.[5]

Lacunar infarctions due to hypertension represent another well studied risk factor in the CKD population.[1] The lacunes do not have to be large or lead to devastating strokes, but over time the accumulation of lacunar infarctions and SVD lead to the observed cognitive decline in CKD and ESRD patients.[5]

It has been known for some time that retinal pathology mirrors kidney pathology, and this is perhaps more generalizable in that neuronal pathology can mirror renal pathology.[5] Given the strong dependence of both organs on vascular blood supply, it seems they are vulnerable to similar insults.[5] Vascular supply must be high and both the kidneys and the brain require a low resistance system.[59] The use of blood flow autoregulation is remarkably similar in the brain and the kidneys, and the perforating arterioles provide this autoregulatory mechanism to keep blood flow constant despite high and low fluctuations of blood pressure.[60] Diabetes in effecting vascular organs, has a profound effect on cerebral and renal function.[1] The vascular changes seen in both the kidneys and the brain with aging are likely the culprit of the ailments of aging seen in both organ systems.[60] Despite the expected correlation between the kidneys and brain, the changes seen in cerebral function in CKD are unusually potent and not explained by just vascular changes alone.[60]

## Nontraditional mediators of cerebrovascular disease in CKD patients

Nontraditional risk factors for cerebrovascular injury include small vessel disease, hyperphosphatemia, vascular calcifications, elastinolysis, chronic inflammation, blood pressure variations, and platelet dysfunction are other nontraditional mediators of cerebrovascular disease.[1,5,60,61] These humoral and chemical factors seem to exert their malign influence on cerebral function via endothelial dysfunction, the effect of uremic solutes, and chronic inflammation. SVD is particularly affected by these mechanisms.[1] White matter changes/hyperintensities have been noted to be more present in CKD patients, and these lesions generally represent neuronal demyelination.[1] This is termed Leukariosis and it is an important associated imaging sign with the epidemiological outcomes of stroke risk, dementia risk, and mortality.[1]

## Small vessel disease (SVD)

Subclinical SVD has been hypothesized to produce cognitive decline, and the syndromic features of cognitive impairment in CKD suggest an organized process.[1] It generally affects executive function and decreased speed in information processing. SVD can also produce lipohylanosis of the subcortical penetrating arteries, which is also linked to defective cerebral circulation autoregulation discussed below.[1] A common feature of SVD is the presence of low grade ischemia sustained over long periods of time.[1]

## Arteriosclerosis

Arteriosclerosis in a volume overloaded patient with defective RAAS signaling is expected, and in CKD, decreased autoregulation and blood pressure spikes and drops likely contribute to chronic cerebral damage in CKD.[5] The anatomy of the cerebral microcirculation is sensitive to these fluctuations, like the kidney. The arteriosclerosis can result in cerebral blood flow diminution leading to a risk of ischemia.[5] The hardening of the renal vasculature as well likely results in impaired control of glomerular pressure and chronic damage to the glomerulus.[5] Variability and arteriosclerosis ultimately may result in increased risk of cerebral microbleeds.[5] It appears that cooling of dialysate may have a salutary effect in preventing white matter changes, sodium changes during dialysis however may promote deleterious cerebral changes.

## Hyperphosphatemia

Hyperphosphatemia is a crucial pathophysiological event, and its worsening sets off many deleterious cascades in the patient with CKD. Parathyroid hormone dysregulation, phosphatonin hypersecretion, medial intimal calcification, bone mineral disease, surreptitious inflammation leading to protein energy wasting.[62–65] All these processes are hallmarks of the physiologic effects of high serum phosphorous.

## Vascular calcification

It is noted that most cardiac lesions in the large number of CKD patients with cardiac lesions are heavily calcified. A similar pattern is seen in patients with cerebrovascular disease and CKD. The process of medial intimal calcification, calciphylaxis on a macroscopic scale, occurs in the vasculature on a microscopic level.[63] This is due to the induction of osteogenic factors like SM22 alpha actin in vascular smooth muscle cells (VSMC). These changes involve type II sodium phosphate co transporters PiT-1 and PiT-2 that can induce VSMC apoptosis.[1] The relationship between poor VSMC health and cerebral infarction risk can be demonstrated in Notch3 mutations where by ailing VSMC place patients at a very high risk of cerebral infarction.[1] A CKD/ESRD related vascular dementia was thought to be caused by a slow process of vascular calcification.[62–65]

The loss of calcification inhibitors like Matrix Glutamate Protein (MGP), pyrophosphate, Fetuin A also results in increased vascular calcification. Matrix metalloproteinases[2] and [9] are also increased in the uremic milieu and are thought to compare to vascular dysfunction.[1] The dysfunction, calcification, and abnormal stiffness of CKD cerebral vascular networks contribute to the risk of ischemic stroke and hemorrhagic stroke. The FGF23 receptor (Klotho) has also been associated with increased stroke risk, with certain alleles (KL-VS) noted in the Ashkenazi Jewish population being associated with early onset stroke. This implicates the phosphatonins pathway in arterial calcification that affects both the neurological and the nephrological vasculature's function.[1,5]

## Elastinolysis

Another factor affected by CKD is the loss of elastin in the walls of arterioles, caused by the same osteogenic gene activation that leads to medial intimal calcification. This is also caused by another mechanism the increase in elastolytic enzymes in high uremic toxin environments. The degraded elastin not only damages the vasculature structurally, but can attract the deposition of hydroxyapatite.[1]

The vascular inflammation resulting from CKD has also been implicated in causing intestinal epithelial barrier breakdown in animal models of CKD. This has been hypothesized to increase gut bacterial translocation, and gut toxin translocation to the systemic circulation. Urea is hypothesized to contribute to systemic vascular inflammation causing the effects on the gastrointestinal tract of patients with advanced CKD and ESRD.[1,5,60] In addition to inflammation, the gut microbiome is also altered leading to production of uremic toxins. These include indoxyl sulfate, trimethylamine-N-oxide (TMAO), and p-cresyl sulfate; and it is known that these toxins are directly related to the observed systemic inflammation and lead directly to increased mortality in advanced CKD/dialysis populations.[1,5,60]

In addition to the renal-gut axis, gut-brain axis connections are now increasingly appreciated. Changes in the gut microbiome have been linked to increased risk of ischemic stroke in a Chinese cohort.[1] TMAO's role is also complex at this point having been reported to be lower in patients with cerebrovascular events than in patients with asymptomatic atherosclerosis.[1]

In addition to the classic risk factor of hypertension, a closely linked but distinct toxicity exists in CKD/ESRD due to salt retention. The salt avid state achieved in CKD and in ESRD result in worsening hypertension additive to the hypertension that already exists in CKD V/ESRD.[66] The combination can often result in malignant hypertension, particularly if patients are fed a high salt diet. This mirrors data from animal studies suggesting this multi layered model in hypertension in dialysis patients.[1,66] NaCl intake is known to contribute to the formation of reactive oxygen species, and interestingly the level of sheer stress from hypertension can also trigger endothelial damage that is believed to be the precursor to malignant hypertension.[67–69] The proinflammatory state from malignant hypertension is also thought to increase Intracellular adhesion molecule -1 which has been linked with white matter hyperintensities. Additionally, blood brain barrier (BBB) disruption is also known to be caused by hypertension.[1]

## Blood pressure variations

Like the renal vascular circuit, the cerebral vascular circuit is a low-pressure circulation and depends on autoregulation to prevent high glomerular pressures.[1,5,60,70,71] It is also notable that advanced cellular architecture guard the compartmentalization of both cerebral and renal cells.[1] The neuronal-capillary interface (or the blood brain barrier), has a homologous function to the glomerular kidney membrane/slit diaphragm/podocyte filter layer (the blood – urine barrier). As well as the aforementioned hypertension associated BBB disruption, SVD in CKD/ESRD can result in an increased level of BBB breakdown due to uremia.[1] This maybe a direct link between uremic toxin increase, BBB dysfunction, and is corroborated by basic science studies showing BBB breakdown in uremic animal models.[1]

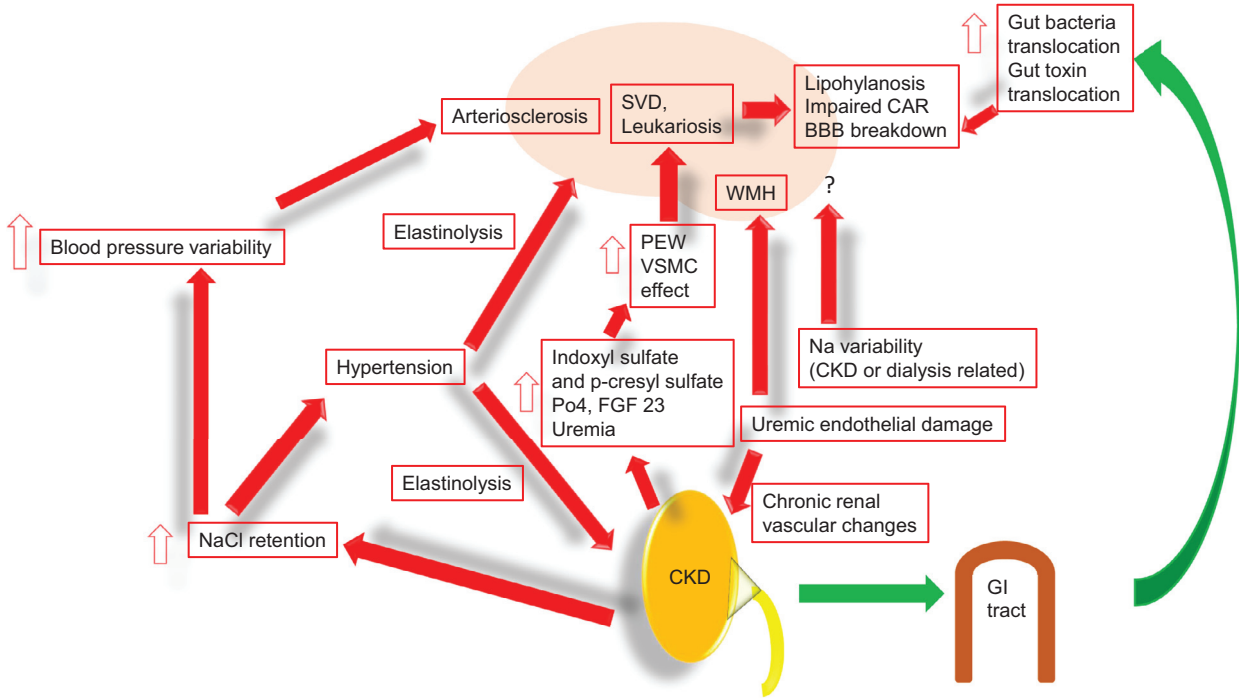


**Fig. 2.** *Interplay of the pathophysiology of CKD contributing to cerebrovascular disease. CKD, Chronic Kidney Disease; FGF-23; fibroblast growth factor 23; GI, gastrointestinal; NaCL, sodium chloride; PEW, protein energy wasting; Po4, phosphates; SVD, small vessel disease; VSMC, vascular smooth muscle; WMH, white matter hyperintensities.*

**Table 1.** *Renal Mediators of Cerebrovascular Disease.*

| *Traditional Mediators of Cerebrovascular Disease* | *Non-Traditional Mediators of Cerebrovascular Disease* |
|---|---|
| Cholesterol related atherosclerosis | Small vessel disease |
| Hypertension | Arteriosclerosis |
| Large vessel disease | Hyperphosphatemia |
| | Vascular calcification |
| | Elastionlysis |
| | Chronic inflammation |
| | Blood pressure variations |
| | Platelet dysfunction |

This development may help explain why the CKD populations have increased cerebrovascular events with CKD/ESRD above that predicted by other risk factor profiles (diabetes, hypertension, hyperlipidemia, obesity, etc).[1] Notably, studies have also shown a direct neurontoxic effect of Indoxyl sulfate and p-cresly sulfate on mouse brain endothelial cells.[5] This also includes a direct cytoskeleton dysregulation effect caused by aberrant phosphorylation of myosin light chains by the MEK-ERK kinase complex.[5]

## Platelet dysfunction

Cerebral microbleeds are a commonly seen complication in the CKD population that is complex because it can be present in the general population with HTN.[5] In CKD patients are reported to be more common in patients with SVD, and are independently predicted by a decreased eGFR.[5] This event may present a proverbial "canary in a coal mine" as the presence of a microbleed augurs a clinically significant hemorrhagic stroke 5 years later.[5] In diabetic patients as well (and many of CKD patients have comorbid DM2), the presence of advanced glycosylation end products is also thought to trigger vascular inflammation that may contribute to the above factors in making a microbleed more likely.[5] While the serum contains receptors for advanced glycosylation end products (sRAGE), they can be saturated.[5] The complex phenomenon of cerebral microbleeds can be caused by comorbid conditions associated with CKD/ESRD, and is directly contributed to by uremic toxins, and diabetic glycosylation end products.[5] This explains the role of uremia/CKD in increasing

risks of CVAs above what maybe predicted by age, gender, and other comorbidities.[5]

## Conclusions

The complex interplay between CKD and cerebrovascular disease is primarily caused by the fact that both the kidney and the brain have strong similarities in vascular organization.[72] The kidneys and the brain are highly vascular organs and any vascular inflammation is highly likely to have end organ effects in both systems (1, 5, 60). In summary comorbid conditions like hypertension, hyperlipidemia, and diabetes contribute to cerebrovascular and renal disease. Sodium fluctuations and blood pressure variability are examples of other deleterious effects arising from a lack of homeostatic constancy.[73,74] In addition to these traditional risk factors, arteriosclerosis, elastinolysis, SVD, hyperphosphatemia, medial intimal calcification, secondary hyperparathyroidism, loss of elastin, loss of calcification inhibitors, gut bacterial translocation, and BBB integrity disruption due to the brain-kidney and the gut-brain axes.[5, 62–65] Finally uremia and its interplay with platelet function,[75] cerebral microbleeds, and endothelial toxicity and inflammation being experienced by endothelial cells are also examples of renal-cerebral interactions resulting in bleeds, strokes, lacunes, white matter hyperintensities, and likely functional cognitive difficulties that result to the brains of patients on chronic dialysis(1, 5,[41] 60) (Fig. 2, Table 1).

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