



# Kidney Disease & Cognitive Impairment

## AN UNDERRECOGNIZED CONNECTION

**Y**ou probably don't give your kidneys much thought. But the bean-shaped, fist-sized organs below your rib cage on each side of your spine filter about 142 litres or 150 quarts of blood daily, removing toxins and extra fluid from your blood so you can excrete them in urine.

Your kidneys maintain a healthy balance of salts, minerals, and water in your blood and also make hormones that control blood pressure, make red blood cells, and keep your bones strong.

People with kidney disease have damaged kidneys that no longer filter blood properly. You may already know that rising waste products in the blood can cause serious health complications, including high blood pressure, cardiovascular disease, anemia, weak bones, nerve damage, and poor nutritional health. Left untreated, kidney disease →

can progress to kidney failure, requiring life-saving kidney replacement treatment with dialysis or kidney transplantation.

## *You may not realize there is a link between kidney disease and cognitive impairment and dementia.*

In this article, we share the latest evidence on the connection between kidney disease and cognitive impairment, explain why it matters, and discuss promising new technology researchers are using to learn more about the nature of neurological deficits in patients requiring dialysis.

### HOW UREMIC TOXINS AFFECT BRAIN HEALTH

In their 2019 literature review in *Brazilian Journal of Nephrology*, researchers identified the following relationships between uremic toxins and various cognitive domains:

- ▶ uric acid: poorer attention, visual processing speed, and working memory;
- ▶ indoxyl sulphate and p-cresyl sulphate: poorer cognitive function in early stages of chronic kidney disease;
- ▶ homocysteine: greater cognitive and motor impairment, especially regarding frontal-executive function, attention, verbal memory, fine motor speed, processing speed, episodic memory, and visual, spatial, language, and constructional ability;
- ▶ interleukin 1-beta: impairments in multiple domains;
- ▶ interleukin 6: poorer executive function, aging processes, degeneration of interneurons responsible for processing, encoding, and retrieving information, and problems with auditory recognition memory, attention memory, and working memory, but not general memory; and
- ▶ parathyroid hormone: increased brain circulating and neuronal calcium levels causing changes in brain function, reduced cerebral blood flow, and behavioural and motor abnormalities.

## KIDNEY DISEASE AND DEMENTIA

According to a review paper by nephrologists at Tufts Medical Center in Boston, published in *American Journal of Kidney Disease* in 2019, as many as 40% of people with chronic kidney disease (CKD) have cognitive impairment, and people with CKD have a substantially higher risk for cognitive deficits than the general population.

The overall prevalence and magnitude of cognitive dysfunction in people with CKD have been controversial. Researchers at Queen's University and Kingston Health Sciences Centre (KHSC) in Kingston, Ontario, conducted a meta-analysis and systematic review of 148 published, peer-reviewed articles to shed light on the degree of cognitive decline in people with CKD.

Dr. Jessica Vanderlinden, then a PhD candidate, and her research supervisor Dr. Gord Boyd, an associate professor of neurology at Queen's University and a critical care doctor and neurologist at KHSC, published the results of their study in *Nephrology* in 2019.

Pre-dialysis and dialysis patients had significant deficits in global functioning, attention, and processing speed compared with people without kidney disease, according to scores on common cognitive assessments such as the Mini-Mental State Examination (MMSE).

However, the average MMSE score for these patients as a group was above the standard cut-off for identifying cognitive impairment, meaning the MMSE was not sensitive enough to identify cognitive deficits in many individuals.

"The MMSE is convenient and quick to administer, but it is heavily weighted toward attention, language, and memory and only includes one point for the perceptual-motor domain," said Dr. Boyd.

In his virtual Grand Rounds presentation for the Ottawa Hospital in April 2023, Dr. Boyd shared a compelling photo to underscore the importance of finding a better method for assessing cognitive dysfunction in patients with CKD.

The image showed a very banged up car parked in the hospital parking garage in the spot allocated for dialysis patients. The adjacent pillars were scratched and chipped, indicating many vehicles had hit them. "The photo illustrates that the degree of visual-spatial and executive function impairment experienced by dialysis patients is quite pronounced and interferes with their daily lives," Dr. Boyd said.

In their review paper, the nephrologists at Tufts Medical Center speculated that the higher rate of cerebrovascular disease in individuals with CKD is likely driving the association with dementia. They also said toxic substances that build up in the blood as kidney function declines, called uremic toxins, depression,

## KIDNEY FUNCTION TESTS

Early kidney disease usually has no symptoms, and 40% of people with severely reduced kidney function who are not on dialysis are unaware they have chronic kidney disease (CKD), according to the Centers for Disease Control and Prevention.

The most common causes of CKD are diabetes and high blood pressure. The National Kidney Foundation advises that long-term, high-dose use of pain medicines, such as ibuprofen, naproxen, and higher dose aspirin, can cause CKD.

Kidney function testing is essential, especially if you have diabetes, high blood pressure, heart disease, or a family history of kidney failure. Ask your doctor if kidney function tests are included as part of your annual physical. Early diagnosis means faster access to treatment to help protect your kidneys from further damage.

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), your doctor will use these tests to check how well your kidneys are functioning:

- A blood test to calculate your estimated glomerular filtration rate (GFR) based on the levels of creatine in your blood, a waste product of normal muscle breakdown in your body. A GFR of 60 or higher is considered in the normal range, while less than 60 may indicate you have kidney disease. A GFR of 15 or less indicates kidney failure. Most individuals with a GFR below 15 need dialysis or a kidney transplant.
- A urine test to measure the presence of albumin, a protein that indicates kidney damage. Healthy kidneys don't let albumin pass into urine, so less albumin in urine indicates better kidney health. The urine albumin-to-creatinine ratio estimates how much albumin passes in urine over 24 hours. A urine albumin-to-creatinine ratio of 30 mg/g or less is normal, while more than 30 mg/g may indicate kidney disease.

Keep in mind that a decline in kidney function is normal as you age and may not be a sign of kidney damage, according to the National Kidney Foundation. You're born with about a million nephrons in each kidney but lose some over time, and others may not function as well as when you were younger. Your doctor will provide guidance on your test results.

sleep disturbances, anemia, and taking multiple prescription medications may also be contributing factors.

Researchers from Brazil published a literature review in *Brazilian Journal of Nephrology* in 2019, that summarized the specific impact of uremic toxins on different cognitive domains. They wrote that the uremic toxins likely harm cognitive function in two ways: direct neurotoxicity and harm to the cerebral endothelium, the latter resulting in oxidative stress, disruption of the blood-brain barrier, and chronic inflammation.

## DETECTING COGNITIVE IMPAIRMENT IN PATIENTS WITH END-STAGE KIDNEY DISEASE

Studies have shown that cognitive impairment is highest among individuals with kidney failure requiring dialysis. "There is a complex interplay between the brain and the kidneys. Hypertension, diabetes, elevated cholesterol, and smoking are shared risk factors between kidney disease and brain disease. CKD adds additional

burdens on brain health in the forms of persistent inflammation, chronic uremia, and arterial stiffness," said Dr. Boyd.



*Dialysis has further negative impacts on the brain, including recurring reduced blood flow, white matter damage, and a loss of nerve fibres that carry messages.*

Dr. Boyd has been testing whether a new technology called the Kinesiographical Instrument for Normal and Altered Reaching Movement (KINARM) device can more accurately detect cognitive deficits in intensive care patients with CKD and acute kidney injury than a standard assessment. —>

KINARM combines robotics and brain injury assessment technology. The patient dons a virtual reality visor and uses hand-held controls to perform a series of ten tasks, such as reaching for a target, interacting with a ball, or tracing a trail through a sequence of targets. The KINARM device tracks and measures their movements, providing support and resistance as required, and takes about 45 to 60 minutes to complete.

Dr. Stephen Scott, a professor in the Department of Biomedical and Molecular Sciences at Queen's University, invented KINARM to study how different brain regions are involved in motor control and learning. The technology is based on the fact that upper limb movement provides robust information about brain function.

Over time, he developed tests for analyzing a broad range of brain functions, including motor skills, memory, decision-making, and perception. KINARM software compares participants' test results with those of healthy individuals to identify impairments in numerous domains, including perceptual-motor, complex attention, and executive function.

Dr. Boyd and Dr. Vanderlinden used KINARM to quantify neurocognitive impairment in 21 survivors of acute kidney injury, caused mainly by kidney disease, compared with 21 individuals with similar cardiovascular issues but without kidney disease.

While a standard pen and paper assessment called the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) detected impairment in only 5% of patients, KINARM testing revealed 48% of these patients had visuomotor impairments, 50% had attention problems, and 52% showed impaired executive function, compared to 10%, 10%, and 24%, respectively, for the control group. These study results, published in *Nephrology Dialysis Transplantation* in 2021, were the first to prospectively report on neurocognitive function after an episode of acute kidney injury.

**CURRENTLY, THE KINARM DEVICE IS AVAILABLE ONLY FOR CLINICAL RESEARCH TO LEARN ABOUT BRAIN FUNCTION AND DYSFUNCTION IN DIFFERENT PATIENT POPULATIONS.**

For example, Dr. Boyd and another one of his students, Tasha Jawa, in the MD-PhD program at Queen's University, are principal investigators of an observational clinical study in progress called the INCOGNITO-AKI study, which will use this tool.

The study aims to enroll 104 intensive care patients with acute kidney injury who initiate kidney replacement therapy. They are measuring patients' cerebral oxygen saturation with a sensor placed on the forehead to see if this assessment could be useful for predicting the risk for long-term neurocognitive impairment.

Study participants return for KINARM and RBANS testing and brain magnetic resonance imaging scans three months and 12 months after their discharge from the hospital. The investigators are also assessing driving safety, adverse events, and medication adherence at 12 months as further indicators of impairment.

An additional strength of using KINARM to assess cognitive impairment in patients with CKD is that the results are compared to age, sex, and handedness-matched controls.



**GENERALLY SPEAKING, CKD AFFECTS MORE MEN THAN WOMEN, WHICH IS WHY IT'S IMPORTANT TO LOOK AT SEX DIFFERENCES.**

Dr. Boyd explained, "In our initial study looking at KINARM data among CKD patients, being male was an independent risk factor for worse cognitive performance compared with women. The only other demographic factor associated with performance was level of education, which is pretty common in cognition studies."

Clinician scientists continue to investigate new approaches to dialysis to improve patient outcomes, as evidence builds showing older patients undergoing the procedure experience moderate to severe cognitive impairment that affects their quality of life. For example, Dr. Boyd's colleagues are studying whether cooled fluid used for dialysis or providing additional fluids may improve neurological outcomes in ICU patients.

While we await the results of these new developments and further research, the link between kidney and cognitive health is clear, so it's important to be kind to those bean-shaped organs. Your brain depends on it. 🧠

## TAKING CARE OF YOUR KIDNEY HEALTH

Taking care of your kidney health is essential to your overall health and brain health. "Your brain is a bank," Dr. Boyd said. "The more you invest in healthy habits earlier in life, the more you have to withdraw later."

Incorporating Women's Brain Health Initiative's Six Pillars of Brain Health, including eating a healthy diet, getting sufficient exercise, managing stress levels to keep inflammation in check, and getting a good night's sleep, will help you maintain good kidney health. "If you have diabetes or high blood pressure, make sure they are well-controlled," Dr. Boyd said. "And keep doing your crossword puzzles."