REVIEW

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Cognitive impairment in chronic kidney disease: role of brain imaging, functional imaging, electroencephalography, cerebrospinal fluid biomarkers and sensors

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ABSTRACT

Chronic kidney disease is associated with cognitive impairment although the underlying mechanisms are still not fully understood. Characterization and efficient monitoring of the cognitive impact of kidney disease and ensuing therapies are critical for the accurate clinical management of patients. A vast array of imaging modalities, biomarkers, and sensors have shown relevance for the assessment of cognitive impairment. Knowing the potential and limitations of these paraclinical techniques is a necessary condition to improve the understanding of this phenomenon and to design monitoring protocols and guidelines applicable to this clinical population. The goal of this review is to provide an overview of current imaging modalities and biomarker sources available to the community, for the benefit of the research and clinical community.

Keywords: brain imaging, CKD, CSF biomarkers, EEG, functional imaging

INTRODUCTION

Chronic kidney disease (CKD) has been known for a long time to be associated with cognitive impairment, but many questions remain about the underlying causes and how to establish assessment and monitoring approaches that are robust, reproductible, and feasible. A wide variety of imaging and physiological biomarkers have been considered as potentially useful for the cognitive assessment of CKD patients, including early diagnosis of subclinical cognitive effects. This review covers magnetic resonance and isotopic imaging, electroencephalography, cerebrospinal fluid and blood biomarkers, as well as sensor-based devices, aiming to present a comprehensive, albeit far from exhaustive, summary of available resources applicable to the investigation and monitoring of CKD-related cognitive effects, as well as the relevant biomarkers that each modality allows to extract (Fig. 1). We strongly advocate that the research and clinical community should collaborate towards exploring the potential and complementary nature of the described modalities.

MAGNETIC RESONANCE IMAGING

Today, magnetic resonance imaging (MRI) studies represent an essential part of the diagnostic approach to neurocognitive disorders (NCD) [1]. In addition to differential diagnosis, MRI biomarkers may detect early, subclinical changes. Advanced brain MR techniques allow the non-invasive assessment of different aspects of brain physiology that can be combined in a single multimodal session [2, 3]. Because no administration of contrast media is needed, these techniques are of particular interest in patients with kidney disease. In the following, the most important modalities and their application in CKD patients will be discussed.

Structural MRI

Structural brain MRI (sMRI) evaluates brain anatomy. It allows the quantitative assessment of whole-brain or region-specific cortical thickness by MR volumetry using high resolution T1-weighted sequences as well as the qualitative assessment of microbleeds and white matter hyperintensities, all of which have

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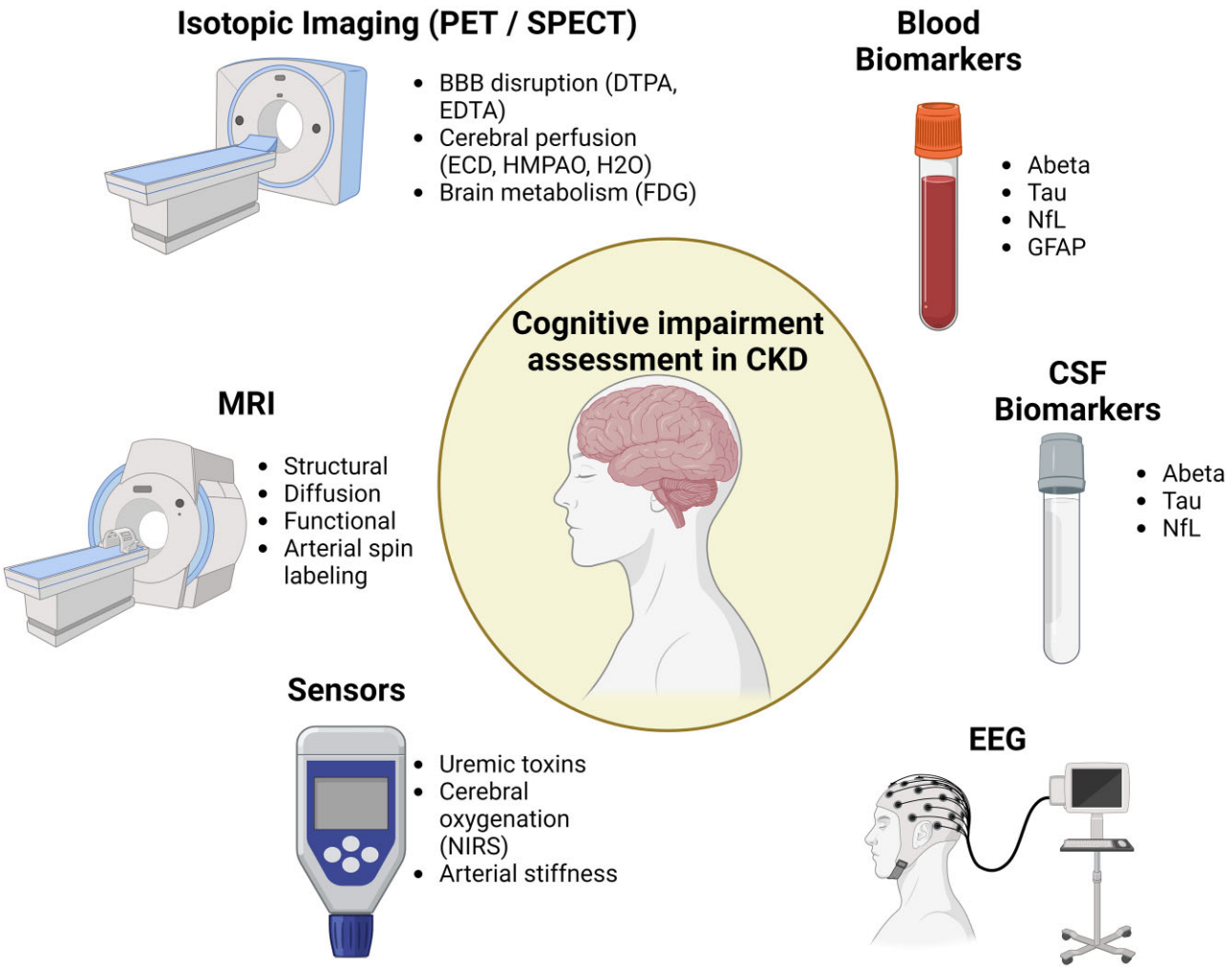

Figure 1: Graphical overview of the modalities covered in this review.

been associated with cognitive decline [4]. In CKD stage 2–5 and kidney transplant recipients, sMRI has consistently revealed signs of small vessel disease including silent brain infarcts, white matter hyperintensities and microbleeds in addition to brain atrophy. Overall, anomalies were correlated with kidney function parameters and improved after kidney transplantation [5–22].

Diffusion MRI

Diffusion MRI relies on a sequence sensitive to the Brownian motion of water molecules. The diffusivity of water protons depends on the adjacent tissue microstructure and may be affected by various disease processes [23]. Main clinical indications of diffusion-MRI therefore include acute brain ischemia, evaluation of brain tumors, and detection of white matter disease. While diffusion-weighted imaging evaluates tissue diffusivity, diffusion tensor imaging (DTI) additionally assesses diffusion directionality and evaluates the integrity of white matter tracts. The main diffusion-derived parameters include the apparent diffusion coefficient and fractional anisotropy (FA), respectively. Similar to the general NCD setting [24, 25], in CKD patients, DTI has shown higher diffusivity and lower FA values, which correlated with clinical cognition markers and were improved after kidney transplantation [12, 16, 22, 26–35].

Arterial spin labeling

Arterial spin labeling (ASL) evaluates cerebral blood flow (CBF) using magnetically labelled water protons as an endogenous tracer through generation of a subtraction image [36]. Altered perfusion patterns may be seen in various disease states including cerebrovascular disease, brain tumors, and epilepsy. Given the relationship between cerebral perfusion, brain metabolism, and activity, ASL-derived CBF has been evaluated as a non-invasive functional cognition marker [37]. Indeed, region-specific CBF changes have been reported in dementia subtypes and corresponding prestages [38, 39]. Among patients with CKD and end-stage kidney disease (ESKD), ASL has revealed increased CBF compared with healthy controls and decreased CBF after dialysis start and kidney transplantation. In most studies, CBF correlated with cognitive performance but was, however, strongly influenced by hemoglobin level or hematocrit [16, 35, 40–43].

Functional MRI

Functional magnetic resonance imaging (fMRI) is widely used for the assessment of brain function through the BOLD effect (blood oxygen level dependent). Resting-state fMRI (rs-fMRI) is particularly attractive in this context, because it does not involve the execution of tasks that may prove challenging for patients. A 2018

review [44] highlighted the potential of rs-fMRI to probe the mechanisms behind cognitive deficits in Parkinson's disease. Functional connectivity (FC), i.e. the correlation between BOLD time-series extracted from regions of interest, is showcased as a powerful metric. Similar approaches have been applied to the study of other neurodegenerative diseases, including correlation with sMRI and diffusion MRI [45].

Regarding application to CKD, local differences between the activation patterns of children with and without CKD performing a working memory task were demonstrated [46]. Many studies have explored metrics such as regional homogeneity (ReHo) and (fractional) amplitude of low-frequency fluctuations (ALFF), which reflect local physiological effects closely related to connectivity. Liang *et al.* [47] showed local ReHo changes in ESKD patients when compared to controls, whereas Yu *et al.* [48] demonstrated localized differences in ReHo and ALFF between dialysis-dependent and non-dialysis-dependent patients. These studies hinted at a correlation between the imaging metrics and urea and creatinine levels. Correlation-based FC has been shown to differ between young CKD patients and controls, suggesting connectivity deficits in attention circuits, which may represent an early marker of cognitive decline [49].

Two independent groups [50, 51] have shown a correlation between MoCA scores and rs-fMRI metrics in hemodialysis (HD) and non-dialysis patients, respectively. It should be noted that both studies resorted to sophisticated analysis strategies, including FC between resting-state networks, dynamic FC, and structural-functional network coupling.

ISOTOPIC IMAGING

Isotopic imaging enables the non-invasive location of molecular and pathophysiological processes in the body, after injection of a molecule of interest coupled with a radioactive isotope (radiotracer).

Disruption of the blood–brain barrier (BBB) is a complex and important common mechanism to several neurodegenerative diseases and systemic diseases associated with cognitive impairment and could play a major role during cognitive impairment associated with CKD [52]. Brain single-photon emission computed tomography coupled with CT scanner (SPECT/CT) with ^{99m}Tc-diethylene-triamine-penta-acetic acid (DTPA) enables the disruption of the BBB to be visualized and quantified. DTPA is a small aminopolycarboxylic acid, which does not normally cross the intact BBB, and the presence of DTPA in the brain parenchyma reflects BBB rupture. ^{99m}Tc-DTPA brain SPECT/CT is the most used isotopic imaging in pre-clinical studies to evaluate BBB permeability [53, 54], but also in clinical studies [55–57], notably in stroke. Cerebral positron emission tomography (TEP) with ^{68}Ga-EDTA has also been used to quantify BBB disruption in patients [58].

Several models of CKD in rodents showed increased BBB permeability. The BBB disruption, quantified using brain ^{99m}Tc-DTPA SPECT/CT imaging, was correlated with both cognitive impairment and indoxyl sulfate levels [54]. Gupta *et al.* found an increased BBB permeability in ESKD patients [59] compared with control participants, using ^{99m}Tc-DTPA SPECT/CT imaging, but association between cognitive impairment and BBB permeability in CKD patients is yet to be proven. The BREIN study (NCT04328415) [60] confirmed the existence of an increased BBB permeability in ESKD patients undergoing HD and previously undiagnosed for cognitive impairment compared with healthy volunteers matched in age, sex, and education, and its association with cognitive impairment.

Modifications of cerebral perfusion were also described in patients with cognitive impairment using SPECT/CT imaging with various radiotracers such as ^{99m}Tc-ethyl cysteinate dimer (ECD) [61] or ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) [62]. In ESKD patients, HD sessions were associated with a mean decrease of 10%±15% of global and regional CBF, evaluated using ^{15}O-H_2O PET-CT imaging [63].

Brain positron emission tomography (PET) with ^{18}F-flurodeoxyglucose (FDG) enables the study of brain metabolism. It has proven to be useful for early diagnosis of neurodegenerative diseases, and to differentiate between different subtypes of dementia, which display distinct spatial patterns of brain metabolism [64]. For example, patients with Alzheimer's disease (AD) display cortical hypometabolisms, particularly in the frontal, posterior temporal, and parietal regions [65]. It can also help to differentiate between mild cognitive impairment and early-stage AD [66, 67]. However, very few studies have evaluated brain metabolism during CKD, and its association with cognitive impairment in both pre-clinical and clinical studies. Interestingly, patients with pre-dialysis stage 5 CKD and depressive symptoms displayed decreased cerebral glucose metabolism in 18F-FDG PET imaging, especially in the prefrontal cortex [68].

These imaging techniques are not routinely used in clinical practice in CKD patients. However, we suggest that ^{99m}Tc-DTPA SPECT/CT imaging could be used to evaluate the BBB disruption in CKD patients, notably in the context of cognitive troubles, and the risk of neurological events. Indeed, BBB disruption could also increase drug neurotoxicity and predisposition to stroke in these patients [52]. Also, brain PET with FDG could help differentiate CKD-induced MCI from other neurodegenerative diseases like AD, along with MRI, in CKD patients displaying cognitive impairment.

ELECTROENCEPHALOGRAPHY

In comparison to other imaging methods, electroencephalography (EEG) stands out as a wearable cost-effective tool. Event-related potentials (ERPs) are stimulus-evoked signals hidden in natural EEG, with early peaks reflecting detection and basic processing stages and later ones reflecting higher-level cognitive processes such as attention, memory, and executive function. In cases of cognitive decline, ERP features will become disrupted.

EEG has been used to study the central nervous system functioning of CKD patients for decades. Marsh *et al.* [69] observed abnormally high latency and low amplitude of later ERP components in CKD patients compared with normal subjects, suggesting less effective cognitive processing. Subsequent ERP studies have revealed reduced latency and increased amplitude after the HD treatment session [70, 71]. In a study conducted by Madan *et al.* [72], ERPs were measured two hours before and after the HD treatment and juxtaposed with data from healthy controls. The healthy group demonstrated the lowest mean auditory P3 latency, while the CKD patients exhibited a significantly prolonged latency pre-HD, a disparity that was diminished substantially following the HD. While the shorter latency indicates better cognitive processing, Michałowski *et al.* [73] observed that behavioral and ERP data indicated action preparation deficits for dialysis patients, which were not observed in kidney transplant and healthy controls.

These findings hint at a potential utility of ERP measures as early markers of cognitive decline. However, integrating cognitive testing into EEG study requires complex equipment and data processing. A resting state EEG approach may offer a more feasible

solution for cognitive assessment. Florea *et al.* [74] reported that HD caused slowing of the EEG background activity. However, the changes were related to younger age, recent initiation of HD therapy and the level of uremia, which seem to refer to the dialysis disequilibrium syndrome (DDS). The patients' mild symptoms were not classified as DDS, suggesting that EEG enables the detection of even subtle changes below the threshold of DDS. The authors suggest that EEG indicates that the dialysis induced pathomechanisms of CNS [74].

Lizio *et al.* [75] designed a study protocol to investigate the impact of uremic toxins with resting-state EEG signals from four groups: CKD patients at stages 3–4 with mild cognitive impairment (MCI) (CKDMCI-3&4), representing a model of high-level uremic toxins; CKD patients undergoing HD with MCI (CKDMCI-H), representing low/medium levels of uremic toxins; MCI patients with cerebrovascular disease (CVMCI); and healthy controls, both without abnormal levels of uremic toxins. EEG recordings for the HD group were performed between treatment days to avoid acute effects of dialysis. All MCI groups indicated decreased occipital alpha power compared with healthy controls, with the lowest parietal alpha power observed in the CKDMCI-3&4. Additionally, the CKDMCI exhibited increased frontal, central, and parietal delta-theta power compared with the control and CVMCI. The authors concluded that circulating uremic toxins affect brain activity and EEG measures could be used to monitor brain function and the effects of interventions.

The presented studies employed traditional linear methods for EEG signal analysis. However, EEG signals are inherently complex and nonlinear. Päeske *et al.* [76] compared various linear and nonlinear measures and recommended Higuchi's fractal dimension (HFD) as a preferred EEG-based measure due to its ability to capture a broad spectrum of brain disorders. As far as we know, HFD has not been applied to EEG signals of CKD patients. Further research is needed, given the simplicity of single-channel EEG recording and the growing accessibility of certified portable EEG devices.

Today clinicians require support systems providing personalized information to guide treatment decisions for individual patients. Consequently, future research should emphasize longitudinal studies and personalized models. The availability of wearable devices allows EEG data collection during dialysis in the clinic and at home.

CEREBROSPINAL FLUID AND BLOOD BIOMARKERS

Biomarkers [77] are tools used to study MCI, AD, and other neurodegenerative diseases, including: (i) Amyloid plaque markers: Amyloid β peptides 42 (Aβ42) and the ratio of amyloid β peptides 42 to 40 (Aβ42/Aβ40). Low levels of Aβ42 in CSF are associated with the formation of amyloid plaques in the brain, a hallmark of AD. (ii) Tau pathology markers: Total tau (T-tau) and phosphorylated tau (P-tau) are markers of AD-related tau metabolism and phosphorylation. The three main phosphorylated tau proteins are P-tau181, P-tau217, and P-tau231. Hyperphosphorylation causes tau protein to accumulate in neurofibrillary tangles between neurons, thereby disrupting synaptic communication. P-tau181 is a classic AD biomarker. (iii) Neurodegenerative markers: Neurofilament light chain (NfL) is enriched in the axons of large-caliber neurons. Increased concentrations of NfL are seen in multiple neurodegenerative diseases and are considered biomarkers of disease severity. (iv) Glial activation markers: Glial fibrillary acidic protein (GFAP), a marker of astrocyte activation and astrogliosis, is increased in multiple neurodegenerative diseases. Initially, these biomarkers could only be measured in CSF, but advances in technology now make the entire amyloid/tau/neurodegeneration (ATN) [78] panel of AD biomarkers and GFAP available via blood tests [77].

CKD and CSF biomarkers

Studies have shown that CKD increases the risk of MCI, AD, and have suggested a causal direction [79]. The association between CKD and biomarkers is an emerging area of research that is important for understanding the interaction between CKD and neurological diseases, facilitating early diagnosis and tracking disease progression. However, research on the relationship between CKD and CSF biomarkers is limited and has yielded inconsistent results. For instance, two studies—one involving AD patients [80] and the other involving cognitively normal individuals [81]—found that CKD was associated with decreased CSF Aβ and increased CSF levels of T-tau. Conversely, a community-based study from the Gothenburg H70 cohort [82] found no differences in CSF biomarkers (Aβ, Tau, and NfL) between CKD and non-CKD individuals. However, among participants exhibiting Aβ pathology [83], correlations were observed for CSF Aβ42, Aβ42/40, t-tau, and estimated glomerular filtration rate (eGFR).

CKD and blood biomarkers

Several studies have previously explored the relationship between CKD and plasma Aβ levels. In the Mayo Clinic Study of Aging cohort (MCSA) [84], CKD correlated with elevated levels of Aβ42, Aβ40, and Aβ42/40 ratio. Similarly, a study performed under the Atherosclerosis Risk in Communities Study cohort [85] revealed a doubling of the urine albumin-to-creatinine ratio and lower eGFR linked to increased plasma levels of Aβ1–40 and Aβ1–42. Gronewold *et al.* [86] found that plasma Aβ accumulation corresponded to CKD stage, indicating the kidney's pivotal role in Aβ elimination from plasma. Kitaguchi *et al.* [87] investigated plasma tau levels in CKD patients undergoing HD. Regardless of HD, CKD patients exhibited elevated plasma tau concentrations, with tau observed to increase 1-hour post-dialysis. These findings suggest that the kidneys play a role in tau degradation and excretion. However, HD appears ineffective in removing tau from the blood. Two studies from the MCSA cohort demonstrated that CKD correlates with T-tau [84], as well as with P-tau181 and P-tau217 [88] after adjusting for age and sex. In the BALTAZAR study of 476 MCI participants, CKD or eGFR were independently associated with plasma P-tau181 levels, which should be taken into account when using P-tau181 [89] as a diagnostic marker for AD. Several larger studies have previously reported an association between NfL and CKD, including participants from the cognitively normal ESTHER study [90] and the Mayo Clinic Study of Aging [83]. Additionally, in a cohort of cognitively normal Swedish individuals [82], there was a statistically significant correlation between NfL and eGFR. However, in contrast, a recent study of patients from the French MEMENTO [91] cohort did not find any influence of CKD and other vascular complications on the predictive value of circulating NfL for the incidence of dementia during a 5-year follow-up. These findings suggest that the relationship between NfL and CKD may vary across different populations and study designs, indicating the need for further research. The ESTHER study [90] demonstrated stronger associations between eGFR and plasma GFAP, only in men after adjusting for age and sex. GFAP levels and kidney function have been shown to vary according to sex [92].

For many years, the diagnosis of AD was based on clinical criteria. The 2024 NIA-AA criteria [93] now include blood biomarker

testing. The future of precision medicine will likely rely more on blood biomarkers to identify the high-risk population, diagnose diseases, and assess the effectiveness of treatments. Future research on the connection between CKD and blood biomarkers of AD could focus on several areas. For instance, investigating the potential mechanisms by which CKD affects the levels and clearance of blood biomarkers (such as Aβ42, Aβ40, and tau), since understanding these mechanisms can help refine biomarker assessments in CKD patients at risk for AD and adjust relevant cutoff points. Conducting longitudinal studies with representative cohorts to track changes in biomarker levels over time in CKD patients and relate them to cognitive decline and AD onset could clarify causal links and reveal early intervention points. In addition, exploring alternative or improved dialysis technologies that may effectively remove tau and other neurodegenerative biomarkers from the blood, studying the variability of CKD-AD biomarker relationships across different populations, including ethnic and geographic differences, and investigating how CKD impacts AD biomarkers differently in men and women, which could lead to more personalized management strategies for both CKD and AD, are viable research alternatives.

SENSORS

Sensor techniques offer an opportunity for non-invasive, real-time measurement of cognitive impairment parameters-biomarkers in patients with CKD. Wearable and wireless technologies would be advantageous since they allow for unobtrusive and seamless measurements [94]. Parameters related to monitoring cognitive impairment on CKD patients include cerebral hypoperfusion [95], arterial stiffness [96], mobility performance, and levels of uremic toxins [97]. In everyday routine, pervasive remote tools, such as watches and trackers, may provide details on physical activity, estimated caloric expenditure, metabolic data, sleep quality, and vital parameters [98].

Intradialytic cerebral hypoperfusion can occur during routine hemodialysis (HD) due to circulatory stress. Appropriate intradialytic cerebral perfusion monitoring can be seen as a part of cognitive decline prevention strategy. Cerebral tissue oxygenation, measured by near-infrared spectroscopy (NIRS), is known to be decreased in HD patients and is associated with weaker cognitive performance [99]. The NIRS-derived HD cerebral oxygen demand was shown to be associated with intradialytic mean arterial pressure, heart rate, and volume removal in HD patients [100]. Cerebral regional oxygen saturation (rSO2), which can be monitored by NIRS, is associated with cognitive function in non-HD CKD patients [101], and was shown to be affected by eGFR, serum albumin, and sodium concentrations in CKD patients [102]. Also, Hb levels revealed a positive and significant association with cerebral rSO2 and the relationship was proven to be linear [103]. However, patient age and sensor location can affect rSO2 values [104]. Intradialytic cerebral ischemia from cerebral oxygenation during HD, but not hypotension from continuous blood pressure (BP) measurements, correlated with decreased executive cognitive function [105].

The consistent evidence linking systemic arterial stiffness to cognitive decline and dementia has been highlighted by several studies, albeit with inconsistencies due to different study designs (cross-sectional vs. longitudinal), heterogeneity of target populations and cognitive screening tools. In general, higher pulse wave velocity (PWV) estimating systemic arterial stiffness, relevant also for CKD patients [106], predicts poor cognitive performance and a steeper cognitive decline [96].

Mobility performance, as a potential digital biomarker of cognitive impairment among HD patients, including cumulated posture duration (sitting, lying, standing, and walking), daily walking performance (step and unbroken walking bout), as well as postural-transition (daily number and average duration), can be measured using a validated pendant-sensor for a continuous period of 24-hour during a non-dialysis day [107]. Also, speed of ankle rotation, monitored by a wearable sensor during a simple intradialytic cognitive-demanding exercise, has been proposed as a digital biomarker for screening cognitive frailty in HD patients [108]. Motor capacity can be quantified by assessing standing balance and gait performance [107].

Uremic toxins are known to have an impact on cerebrovascular diseases and/or cognition [109–111]. An earlier study suggested that disturbed purine nucleotide metabolism, resulting in hyperuricemia in CKD, is a risk factor for cognitive impairment [97]. Cognitive impairment in ESKD patients in HD, assessed as an increased BBB permeability, could be associated with serum uremic toxins like indoxyl sulfate (NCT04328415), [112] and indole-3-acetic acid [113]. Multicomponent, real-time, and on-line monitoring of uremic toxins can facilitate studies of the associations between cognitive impairment and uremic toxin removal efficiency. A technology for multi-component uremic toxins' intradialytic optical monitoring of spent dialysate [114, 115] demonstrated that optical dialysis monitoring can simultaneously reveal intradialytic removal patterns of low molecular weight and middle uremic retention solutes without any blood or dialysate sampling [116–118]. The small uremic retention solute uric acid is one of the main chromophores [114], and protein-bound uremic retention solute indoxyl sulfate is one of the main fluorophores [115]. Furthermore, time-averaged concentration estimation of uremic toxins, based on intradialytic spent dialysate measurements, has been proposed [119].

Large-scale longitudinal studies have found an association between glycemic control and cognitive decline [120]. Continuous glucose monitoring (CGM) offers benefits in terms of detecting hypoglycemia by measuring glucose in interstitial fluid every few minutes and can provide more reliable method of glycemic assessment, including asymptomatic hypoglycemia and hyperglycemic episodes [121]. Hyperglycemia metrics (mean glycose value and time in range) derived from CGM are shown to be associated with cognitive functions, especially with executive function and working memory, in older adults with type 2 diabetes [122]. However, assessing glycemic control in patients with advanced CKD and on dialysis (G4-5) can be challenging because laboratory biomarkers, such as glycated hemoglobin (HbA_{1c}), may be biased by abnormalities in blood hemoglobin, use of iron therapy and erythropoiesis-stimulating agents, and chronic inflammation due to uremia, etc. [121], and data are scarce in this population. Further studies are needed to investigate in more detail how cognitive decline might be prevented by glycemic control in CKD patients.

CONCLUSION

In this review we aimed to provide an overview of the currently available range of biomarkers and imaging modalities that have shown potential for the detection of cognitive impairment in CKD patients. It is hoped that this review will contribute to collaborative efforts towards the pursuit of pre-clinical and clinical research on this topic and the incorporation of several modalities and biomarkers into protocols, procedures, and guidelines for the reproducible, precise, and clinically relevant assessment of cognitive status in patients with CKD.

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CONFLICT OF INTEREST STATEMENT

None declared

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

APPENDIX

CONNECT collaborators

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REFERENCES

1. Knopman DS, DeKosky ST, Cummings JL *et al.* Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;**56**:1143–53. https://doi.org/10.1212/WNL.56.9.1143
2. Mani LY, Vogt B, Vermathen P. Functional magnetic resonance imaging of the kidney. In: Ponticelli C Visweswaran RK (eds.), *Current Progress in Nephrology*. Mumbai: TreeLife Media (A Div of Kothari Medical), 2022.
3. Mani LY, Seif M, Nikles F *et al.* Hip position acutely affects oxygenation and perfusion of kidney grafts as measured by functional magnetic resonance imaging methods—the bent knee study. *Front Med (Lausanne)* 2021;**8**:697055. https://doi.org/10.3389/fmed.2021.697055
4. Giorgio A, De Stefano N. Clinical use of brain volumetry. *J Magn Reson Imaging* 2013;**37**:1–14. https://doi.org/10.1002/jmri.23671
5. Kobayashi M, Hirawa N, Yatsu K *et al.* Relationship between silent brain infarction and chronic kidney disease. *Nephrol Dial Transplant* 2009;**24**:201–7. https://doi.org/10.1093/ndt/gfn419
6. Li L, Fisher M, Lau WL *et al.* Cerebral microbleeds and cognitive decline in a hemodialysis patient: case report and review of literature. *Hemodial Int* 2015;**19**:E1–7. https://doi.org/10.1111/hdi.12210
7. Vogels SC, Emmelot-Vonk MH, Verhaar HJ *et al.* The association of chronic kidney disease with brain lesions on MRI or CT: a systematic review. *Maturitas* 2012;**71**:331–6. https://doi.org/10.1016/j.maturitas.2012.01.008
8. Yao H, Miwa Y, Takashima Y *et al.* Chronic kidney disease and subclinical lacunar infarction are independently associated with frontal lobe dysfunction in community-dwelling elderly subjects: the Sefuri brain MRI study. *Hypertens Res* 2011;**34**:1023–8. https://doi.org/10.1038/hr.2011.83
9. Chang CY, Lin CC, Tsai CF *et al.* Cognitive impairment and hippocampal atrophy in chronic kidney disease. *Acta Neurol Scand* 2017;**136**:477–85. https://doi.org/10.1111/ane.12753.
10. Freedman BI, Sink KM, Hugenschmidt CE *et al.* Associations of early kidney disease with brain magnetic resonance imaging and cognitive function in African Americans with type 2 diabetes mellitus. *Am J Kidney Dis* 2017;**70**:627–37. https://doi.org/10.1053/j.ajkd.2017.05.006
11. Hartung EA, Erus G, Jawad AF *et al.* Brain magnetic resonance imaging findings in children and young adults with CKD. *Am J Kidney Dis* 2018;**72**:349–59. https://doi.org/10.1053/j.ajkd.2017.11.024
12. Lau WL, Nunes ACF, Vasilevko V *et al.* Chronic kidney disease increases cerebral microbleeds in mouse and man. *Transl Stroke Res* 2020;**11**:122–34. https://doi.org/10.1007/s12975-019-00698-8
13. van der Plas E, Solomon MA, Hopkins L *et al.* Global and regional white matter fractional anisotropy in children with chronic kidney disease. *J Pediatr* 2022;**242**:166–173.e3. https://doi.org/10.1016/j.jpeds.2021.11.006.
14. Yeh YC, Kuo YT, Huang MF *et al.* Association of brain white matter lesions and atrophy with cognitive function in chronic kidney disease. *Int J Geriatr Psychiatry* 2019;**34**:1826–32. https://doi.org/10.1002/gps.5198
15. Khatri M, Wright CB, Nickolas TL *et al.* Chronic kidney disease is associated with white matter hyperintensity volume: the Northern Manhattan Study (NOMAS). *Stroke* 2007;**38**:3121–6. https://doi.org/10.1161/STROKEAHA.107.493593

16. van Sandwijk MS, Ten Berge IJM, Caan MWA *et al.* Cognitive improvement after kidney transplantation is associated with structural and functional changes on MRI. *Transplant Direct* 2020;**6**:e531. https://doi.org/10.1097/TXD.0000000000000976
17. Zheng K, Zhou Y, Qian Y *et al.* Increased premature cerebral small vessel diseases in dialysis patients: a retrospective cross-sectional study. *Nephron* 2021;**145**:330–41. https://doi.org/10.1159/000513121
18. Dong J, Ma X, Lin W *et al.* Aberrant cortical thickness in neurologically asymptomatic patients with end-stage renal disease. *Neuropsychiatr Dis Treat* 2018;**14**:1929–39. https://doi.org/10.2147/NDT.S170106
19. Drew DA, Bhadelia R, Tighiouart H *et al.* Anatomic brain disease in hemodialysis patients: a cross-sectional study. *Am J Kidney Dis* 2013;**61**:271–8. https://doi.org/10.1053/j.ajkd.2012.08.035
20. Weiner DE, Bartolomei K, Scott T *et al.* Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. *Am J Kidney Dis* 2009;**53**:438–47. https://doi.org/10.1053/j.ajkd.2008.08.022
21. Zhang LJ, Wen J, Ni L *et al.* Predominant gray matter volume loss in patients with end-stage renal disease: a voxel-based morphometry study. *Metab Brain Dis* 2013;**28**:647–54. https://doi.org/10.1007/s11011-013-9438-7
22. Vemuri P, Davey C, Johansen KL *et al.* Chronic kidney disease associated with worsening white matter disease and ventricular enlargement. *J Alzheimers Dis* 2021;**83**:1729–40. https://doi.org/10.3233/JAD-210604
23. Le Bihan D, Breton E. Imagerie de diffusion in-vivo par résonance magnétique nucléaire. *C R Acad Sci* 1985;**93**:27–34.
24. Goujon A., Mejdoubi M., Purcell Y. *et al.* Can MRI water apparent diffusion coefficient (ADC) value discriminate between idiopathic normal pressure hydrocephalus, Alzheimer's disease and subcortical vascular dementia? *J. Neuroradiol* 2018;**45**:15–22. https://doi.org/10.1016/j.neurad.2017.08.001
25. Sexton CE, Kalu UG, Filippini N *et al.* A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 2011;**32**:2322 e5–18. https://doi.org/10.1016/j.neurobiolaging.2010.05.019
26. Zhang R, Liu K, Yang L *et al.* Reduced white matter integrity and cognitive deficits in maintenance hemodialysis ESRD patients: a diffusion-tensor study. *Eur Radiol* 2015;**25**:661–8. https://doi.org/10.1007/s00330-014-3466-5
27. Vemuri P, Knopman DS, Jack CR, Jr *et al.* Association of kidney function biomarkers with brain MRI findings: the BRINK study. *J Alzheimers Dis* 2017;**55**:1069–82. https://doi.org/10.3233/JAD-160834
28. Bai Z, Ma X, Tian J *et al.* Brain microstructural abnormalities are related to physiological alterations in end-stage renal disease. *PLoS One* 2016;**11**:e0155902. https://doi.org/10.1371/journal.pone.0155902
29. Chou MC, Ko CH, Hsieh TJ *et al.* A preliminary report of longitudinal white matter alterations in patients with end-stage renal disease: a three-year diffusion tensor imaging study. *PLoS One* 2019;**14**:e0215942. https://doi.org/10.1371/journal.pone.0215942
30. Drew DA, Koo BB, Bhadelia R *et al.* White matter damage in maintenance hemodialysis patients: a diffusion tensor imaging study. *BMC Nephrol* 2017;**18**:213. https://doi.org/10.1186/s12882-017-0628-0
31. Eldehni MT, Odudu A, McIntyre CW. Brain white matter microstructure in end-stage kidney disease, cognitive impairment, and circulatory stress. *Hemodial Int* 2019;**23**:356–65. https://doi.org/10.1111/hdi.12754
32. Guo H, Liu W, Li H *et al.* Structural and functional brain changes in hemodialysis patients with end-stage renal disease: DTI analysis results and ALFF analysis results. *Int J Nephrol Renovasc Dis* 2021;**14**:77–86. https://doi.org/10.2147/IJNRD.S295025
33. Gupta A, Lepping RJ, Yu AS *et al.* Cognitive function and white matter changes associated with renal transplantation. *Am J Nephrol* 2016;**43**:50–7. https://doi.org/10.1159/000444334
34. Hsieh TJ, Chang JM, Chuang HY *et al.* End-stage renal disease: in vivo diffusion-tensor imaging of silent white matter damage. *Radiology* 2009;**252**:518–25. https://doi.org/10.1148/radiol.2523080484
35. Lepping RJ, Montgomery RN, Sharma P *et al.* Normalization of cerebral blood flow, neurochemicals, and white matter integrity after kidney transplantation. *J Am Soc Nephrol* 2021;**32**:177–87. https://doi.org/10.1681/ASN.2020050584
36. Detre JA, Leigh JS, Williams DS *et al.* Perfusion imaging. *Magn Reson Med* 1992;**23**:37–45. https://doi.org/10.1002/mrm.1910230106
37. Haidar H, Majzoub RE, Hajeer S *et al.* Arterial spin labeling (ASL-MRI) versus fluorodeoxyglucose-PET (FDG-PET) in diagnosing dementia: a systematic review and meta-analysis. *BMC Neurol* 2023;**23**:385. https://doi.org/10.1186/s12883-023-03432-y
38. Haller S, Zaharchuk G, Thomas DL *et al.* Arterial spin labeling perfusion of the brain: emerging clinical applications. *Radiology* 2016;**281**:337–56. https://doi.org/10.1148/radiol.2016150789
39. Sierra-Marcos A. Regional cerebral blood flow in mild cognitive impairment and Alzheimer's disease measured with arterial spin labeling magnetic resonance imaging. *Int J Alzheimers Dis* 2017;**2017**:5479597.
40. Liu HS, Hartung EA, Jawad AF *et al.* Regional cerebral blood flow in children and young adults with chronic kidney disease. *Radiology* 2018;**288**:849–58. https://doi.org/10.1148/radiol.2018171339
41. Prohovnik I, Post J, Uribarri J *et al.* Cerebrovascular effects of hemodialysis in chronic kidney disease. *J Cereb Blood Flow Metab* 2007;**27**:1861–9. https://doi.org/10.1038/sj.jcbfm.9600478
42. Jiang XL, Wen JQ, Zhang LJ *et al.* Cerebral blood flow changes in hemodialysis and peritoneal dialysis patients: an arterial-spin labeling MR imaging. *Metab Brain Dis* 2016;**31**:929–36. https://doi.org/10.1007/s11011-016-9829-7
43. Cheng BC, Chen PC, Chen PC *et al.* Decreased cerebral blood flow and improved cognitive function in patients with end-stage renal disease after peritoneal dialysis: an arterial spin-labelling study. *Eur Radiol* 2019;**29**:1415–24. https://doi.org/10.1007/s00330-018-5675-9
44. Li K, Su W, Li S-H *et al.* Resting state fMRI: a valuable tool for studying cognitive dysfunction in PD. *Parkinsons Dis* 2018;6278649.
45. Yue J, Han S, Li A *et al.* Multimodal magnetic resonance imaging on brain structure and function changes in subjective cognitive decline: a mini-review. *Front Aging Neurosci* 2023;**15**:1259190. https://doi.org/10.3389/fnagi.2023.1259190
46. Harrell W, Gipson DS, Belger A *et al.* Functional magnetic resonance imaging findings in children and adolescents with chronic kidney disease: preliminary findings. *Semin Nephrol* 2021;**41**:462–75. https://doi.org/10.1016/j.semnephrol.2021.09.009
47. Liang X, Wen J, Ni L *et al.* Altered pattern of spontaneous brain activity in the patients with end-stage renal disease: a resting-state functional MRI study with regional homogeneity analysis. *PLoS One* 2013;**8**:e71507. https://doi.org/10.1371/journal.pone.0071507

48. Yu H, Zhang C, Cai Y *et al.* Abnormal regional homogeneity and amplitude of low frequency fluctuation in chronic kidney patients with and without dialysis. *Front Neurosci* 2022;**16**:1064813. https://doi.org/10.3389/fnins.2022.1064813
49. Herrington JD, Hartung EA, Laney NC *et al.* Decreased neural connectivity in the default mode network among youth and young adults with chronic kidney disease. *Semin Nephrol* 2021;**41**:455–61. https://doi.org/10.1016/j.semnephrol.2021.09.008
50. Zhang D, Chen Y, Shen J *et al.* Static and dynamic characteristics of functional network connectivity in neurologically asymptomatic patients undergoing maintenance hemodialysis: a resting-state functional MRI study. *J Magn Reson Imaging* 2023;**57**:420–31. https://doi.org/10.1002/jmri.28317
51. Song L, Liu X, Yang W *et al.* Association of aberrant structural-functional network coupling with cognitive decline in patients with non-dialysis-dependent stage 5 chronic kidney disease. *Quant Imaging Med Surg* 2023;**13**:8611–24. https://doi.org/10.21037/qims-23-295
52. Bobot M. Cognitive impairment and the blood-brain barrier in chronic kidney disease: role of the uremic toxins. *Nephrol Ther* 2023;**19**:607–15. https://doi.org/10.1684/ndt.2023.51
53. Garrigue P, Giacomino L, Bucci C *et al.* Single photon emission computed tomography imaging of cerebral blood flow, blood-brain barrier disruption, and apoptosis time course after focal cerebral ischemia in rats. *Int J Stroke* 2016;**11**:117–26. https://doi.org/10.1177/1747493015607516
54. Bobot M, Thomas L, Moyon A *et al.* Uremic toxic blood-brain barrier disruption mediated by AhR activation leads to cognitive impairment during experimental renal dysfunction. *J Am Soc Nephrol* 2020;**31**:1509–21. https://doi.org/10.1681/ASN.2019070728
55. Lorberboym M, Lampl Y, Sadeh M. Correlation of 99mTc-DTPA SPECT of the blood-brain barrier with neurologic outcome after acute stroke. *J Nucl Med* 2003;**44**:1898–904.
56. Lampl Y, Shmuilovich O, Lockman J *et al.* Prognostic significance of blood brain barrier permeability in acute hemorrhagic stroke. *Cerebrovasc Dis* 2005;**20**:433–7. https://doi.org/10.1159/000088981
57. Gilad R, Lampl Y, Eilam A *et al.* SPECT-DTPA as a tool for evaluating the blood-brain barrier in post-stroke seizures. *J Neurol* 2012;**259**:2041–4. https://doi.org/10.1007/s00415-012-6445-2
58. Pozzilli C, Bernardi S, Mansi L *et al.* Quantitative assessment of blood-brain barrier permeability in multiple sclerosis using 68-Ga-EDTA and positron emission tomography. *J Neurol Neurosurg Psychiatry* 1988;**51**:1058–6. https://doi.org/10.1136/jnnp.51.8.1058
59. Gupta A, Bansal A, Young K *et al.* Blood-brain barrier permeability in ESKD—A proof-of-concept study. *J Am Soc Nephrol* 2023;**34**:1508–11. https://doi.org/10.1681/ASN.0000000000000167
60. Bobot M, Guedj E, Resseguier N *et al.* Increased blood-brain barrier permeability and cognitive impairment in patients with ESKD. *Kidney International Reports* 2024;**9**:2988–95. https://doi.org/10.1016/j.ekir.2024.07.021
61. Guedj E, Barbeau EJ, Didic M *et al.* Effects of medial temporal lobe degeneration on brain perfusion in amnestic MCI of AD type: deafferentation and functional compensation? *Eur J Nucl Med Mol Imaging* 2009;**36**:1101–12. https://doi.org/10.1007/s00259-009-1060-x
62. Staffen W, Bergmann J, Schönauer *et al.* Cerebral perfusion (HMPAO-SPECT) in patients with depression with cognitive impairment versus those with mild cognitive impairment and dementia of Alzheimer's type: a semiquantitative and automated evaluation. *Eur J Nucl Med Mol Imaging* 2009;**36**:801–10. https://doi.org/10.1007/s00259-008-1028-2
63. Polinder-Bos HÁ, Vállez Garcia D, Kuipers J *et al.* Hemodialysis induces an acute decline in cerebral blood flow in elderly patients. *J Am Soc Nephrol* 2018;**29**:1317–25. https://doi.org/10.1681/ASN.2017101088
64. Shivamurthy VKN, Tahari AK, Marcus C *et al.* Brain FDG PET and the diagnosis of dementia. *AJR Am J Roentgenol* 2015;**204**:W76–85. https://doi.org/10.2214/AJR.13.12363
65. Meltzer CC, Zubieta JK, Brandt J *et al.* Regional hypometabolism in Alzheimer's disease as measured by positron emission tomography after correction for effects of partial volume averaging. *Neurology* 1996;**47**:454–61. https://doi.org/10.1212/WNL.47.2.454
66. Caroli A, Prestia A, Chen K *et al.* Summary metrics to assess Alzheimer disease-related hypometabolic pattern with 18F-FDG PET: head-to-head comparison. *J Nucl Med* 2012;**53**:592–600. https://doi.org/10.2967/jnumed.111.094946
67. Arbizu J, Prieto E, Martínez-Lage P *et al.* Automated analysis of FDG PET as a tool for single-subject probabilistic prediction and detection of Alzheimer's disease dementia. *Eur J Nucl Med Mol Imaging* 2013;**40**:1394–405. https://doi.org/10.1007/s00259-013-2458-z
68. Song SH, Kim IJ, Kim S-J *et al.* Cerebral glucose metabolism abnormalities in patients with major depressive symptoms in pre-dialytic chronic kidney disease: statistical parametric mapping analysis of F-18-FDG PET, a preliminary study. *Psychiatry Clin Neurosci* 2008;**62**:554–61. https://doi.org/10.1111/j.1440-1819.2008.01849.x
69. Marsh JT, Brown WS, Wolcott D *et al.* Electrophysiological indices of CNS function in hemodialysis and CAPD. *Kidney Int* 1986;**30**:957–63. https://doi.org/10.1038/ki.1986.279
70. Martinez L, Rodriguez M, Bojorges-Valdez E *et al.* Latency and amplitude changes in cognitive event related potentials due to hemodialysis. *Annu Int Conf IEEE Eng Med Biol Soc* 2018;**2018**:2088–91.
71. Gallai V, Alberti A, Buoncristiani U *et al.* Changes in auditory P3 event-related potentials in uremic patients undergoing haemodialysis. *Electromyogr Clin Neurophysiol* 1994;**34**:397–402.
72. Madan P, Agarwal S, Kalra OP *et al.* Effect of hemodialysis on cognitive function in ESRD patients. *Ren Fail* 2007;**29**:699–703. https://doi.org/10.1080/08860220701460103
73. Michałowski JM, Mańkowska A, Heilman KM *et al.* Kidney transplantation and action-intentional improvements: evidence from an ERP study. *Int J Psychophysiol* 2021;**170**:51–8. https://doi.org/10.1016/j.ijpsycho.2021.09.005
74. Florea B, Orasan R, Budurea C *et al.* EEG spectral changes induced by hemodialysis. *Clin Neurophysiol Pract* 2021;**6**:146–8. https://doi.org/10.1016/j.cnp.2021.03.006
75. Lizio R, Lopez S, Babiloni C *et al.* Resting state EEG rhythms in different stages of chronic kidney disease with mild cognitive impairment. *Neurobiol Aging* 2023;**130**:70–9. https://doi.org/10.1016/j.neurobiolaging.2023.05.014
76. Päeske L, Uudeberg T, Hinrikus H *et al.* Correlation between electroencephalographic markers in the healthy brain. *Sci Rep* 2023;**13**:6307. https://doi.org/10.1038/s41598-023-33364-z
77. Hansson O, Edelmayer RM, Boxer AL *et al.* The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement* 2022;**18**:2669–86. https://doi.org/10.1002/alz.12756

78. Hampel H, Cummings J, Blennow K *et al.* Developing the ATX(N) classification for use across the Alzheimer disease continuum. *Nat Rev Neurol* 2021;**17**:580–9. https://doi.org/10.1038/s41582-021-00520-w
79. Viggiano D, Wagner CA, Martino G *et al.* Mechanisms of cognitive dysfunction in CKD. *Nat Rev Nephrol* 2020;**16**:452–69. https://doi.org/10.1038/s41581-020-0266-9
80. Ren JR, Wang Z, Cheng Y *et al.* Associations between plasma klotho with renal function and cerebrospinal fluid amyloid-β levels in Alzheimer's disease: the Chongqing Ageing & Dementia Study. *J Alzheimers Dis* 2023;**92**:477–85.
81. Sun HL, Yao XQ, Lei L *et al.* Associations of blood and cerebrospinal fluid aβ and tau levels with renal function. *Mol Neurobiol* 2023;**60**:5343–51. https://doi.org/10.1007/s12035-023-03420-w
82. Dittrich A, Ashton NJ, Zetterberg H *et al.* Association of chronic kidney disease with plasma NfL and other biomarkers of neurodegeneration: the H70 birth cohort study in Gothenburg. *Neurology* 2023;**101**:e277–e88. https://doi.org/10.1212/WNL.0000000000207419
83. Hansson O, Zetterberg H, Buchhave P *et al.* Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study. *Lancet Neurol* 2006;**5**:228–34. https://doi.org/10.1016/S1474-4422(06)70355-6
84. Syrjanen JA, Campbell MR, Algeciras-Schimnich A *et al.* Associations of amyloid and neurodegeneration plasma biomarkers with comorbidities. *Alzheimers Dement* 2022;**18**:1128–40. https://doi.org/10.1002/alz.12466
85. Sedaghat S, Ji Y, Hughes TM *et al.* The association of kidney function with plasma amyloid-β levels and brain amyloid deposition. *J Alzheimers Dis* 2023;**92**:229–39. https://doi.org/10.3233/JAD-220765
86. Gronewold J, Klafki HW, Baldelli E *et al.* Factors responsible for plasma β-amyloid accumulation in chronic kidney disease. *Mol Neurobiol* 2016;**53**:3136–45. https://doi.org/10.1007/s12035-015-9218-y
87. Kitaguchi N, Tatebe H, Sakai K *et al.* Influx of tau and amyloid-β proteins into the blood during hemodialysis as a therapeutic extracorporeal blood amyloid-β removal system for Alzheimer's disease. *J Alzheimers Dis* 2019;**69**:687–707. https://doi.org/10.3233/JAD-190087
88. Mielke MM, Dage JL, Frank RD *et al.* Performance of plasma phosphorylated tau 181 and 217 in the community. *Nat Med* 2022;**28**:1398–405. https://doi.org/10.1038/s41591-022-01822-2
89. Lehmann S, Schraen-Maschke S, Vidal JS *et al.* Plasma phosphorylated tau 181 predicts amyloid status and conversion to dementia stage dependent on renal function. *J Neurol Neurosurg Psychiatry* 2023;**94**:411–9. https://doi.org/10.1136/jnnp-2022-330540
90. Stocker H, Beyer L, Trares K *et al.* Association of kidney function with development of Alzheimer disease and other dementias and dementia-related blood biomarkers. *JAMA Netw Open* 2023;**6**:e2252387. https://doi.org/10.1001/jamanetworkopen.2022.52387
91. Planche V, Bouteloup V, Pellegrin I *et al.* Validity and performance of blood biomarkers for Alzheimer disease to predict dementia risk in a large clinic-based cohort. *Neurology* 2023;**100**:e473–e84. https://doi.org/10.1212/WNL.0000000000201479
92. Benedet AL, Milà-Alomà M, Vrillon A *et al.* Differences between plasma and cerebrospinal fluid glial fibrillary acidic protein levels across the Alzheimer disease continuum. *JAMA Neurol* 2021;**78**:1471–83. https://doi.org/10.1001/jamaneurol.2021.3671
93. Jack CR, Jr, Andrews JS, Beach TG *et al.* Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement* 2024;**20**:5143–69. https://doi.org/10.1002/alz.13859
94. Dias D, Cunha JPS. Wearable health devices—Vital sign monitoring, systems and technologies. *Sensors (Basel)* 2018;**18**:2414. https://doi.org/10.3390/s18082414
95. Wolfgram DF. Intradialytic cerebral hypoperfusion as mechanism for cognitive impairment in patients on hemodialysis. *J Am Soc Nephrol* 2019;**30**:2052–8. https://doi.org/10.1681/ASN.2019050461
96. Iulita MF, Noriega de la Colina A, Girouard H. Arterial stiffness, cognitive impairment and dementia: confounding factor or real risk? *J Neurochem* 2018;**144**:527–48. https://doi.org/10.1111/jnc.14235
97. Mazumder MK, Phukan BC, Bhattacharjee A *et al.* Disturbed purine nucleotide metabolism in chronic kidney disease is a risk factor for cognitive impairment. *Med Hypotheses* 2018;**111**:36–9. https://doi.org/10.1016/j.mehy.2017.12.016
98. Canaud B, Davenport A, Leray-Moragues H *et al.* Digital health support: current status and future development for enhancing dialysis patient care and empowering patients. *Toxins* 2024;**16**211. https://doi.org/10.3390/toxins16050211
99. Kovarova L, Valerianova A, Kmentova T *et al.* Low cerebral oxygenation is associated with cognitive impairment in chronic hemodialysis patients. *Nephron* 2018;**139**:113–9. https://doi.org/10.1159/000487092
100. Wong A, Robinson L, Soroush S *et al.* Assessment of cerebral oxygenation response to hemodialysis using near-infrared spectroscopy (NIRS): challenges and solutions. *J Innov Opt Health Sci* 2021;**14**:2150016. https://doi.org/10.1142/S1793545821500164
101. Ookawara S, Ito K, Sasabuchi Y *et al.* Cerebral oxygenation and body mass index association with cognitive function in chronic kidney disease patients without dialysis: a longitudinal study. *Sci Rep* 2022;**12**:10809. https://doi.org/10.1038/s41598-022-15129-2
102. Miyazawa H, Ookawara S, Ito K *et al.* Association of cerebral oxygenation with estimated glomerular filtration rate and cognitive function in chronic kidney disease patients without dialysis therapy. *PLoS One* 2018;**13**:e0199366. https://doi.org/10.1371/journal.pone.0199366
103. Ookawara S, Ito K, Sasabuchi Y *et al.* Associations of cerebral oxygenation with hemoglobin levels evaluated by near-infrared spectroscopy in hemodialysis patients. *PLoS One* 2020;**15**:e0236720. https://doi.org/10.1371/journal.pone.0236720
104. Kishi K, Kawaguchi M, Yoshitani K *et al.* Influence of patient variables and sensor location on regional cerebral oxygen saturation measured by INVOS 4100 near-infrared spectrophotometers. *J Neurosurg Anesthesiol* 2003;**15**:302–6. https://doi.org/10.1097/00008506-200310000-00002
105. MacEwen C, Sutherland S, Daly J *et al.* Relationship between hypotension and cerebral ischemia during hemodialysis. *J Am Soc Nephrol* 2017;**28**:2511–20. https://doi.org/10.1681/ASN.2016060704
106. Blacher J, Guerin AP, Pannier B *et al.* Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999;**99**:2434–9. https://doi.org/10.1161/01.CIR.99.18.2434
107. Zhou H, Al-Ali F, Wang C *et al.* Harnessing digital health to objectively assess cognitive impairment in people un-

dergoing hemodialysis process: the impact of cognitive impairment on mobility performance measured by wearables. *PLoS One* 2020;**15**:e0225358. https://doi.org/10.1371/journal.pone.0225358

108. Park C, Al-Ali F, Zhou H *et al.* A practical solution to screen cognitive frailty among hemodialysis patients using a game-based intradialytic exercise with wearable sensors. *Nephrol Dial Transplant* 2021;**36**:gfab091.004. https://doi.org/10.1093/ndt/gfab091.004
109. Bugnicourt JM, Godefroy O, Chillon JM *et al.* Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. *J Am Soc Nephrol* 2013;**24**:353–63. https://doi.org/10.1681/ASN.2012050536
110. Watanabe K, Watanabe T, Nakayama M. Cerebro-renal interactions: impact of uremic toxins on cognitive function. *Neurotoxicology* 2014;**44**:184–93. https://doi.org/10.1016/j.neuro.2014.06.014
111. Chillon JM, Massy ZA, Stengel B. Neurological complications in chronic kidney disease patients. *Nephrol Dial Transplant* 2016;**31**:1606–14. https://doi.org/10.1093/ndt/gfv315
112. Lin YT, Wu PH, Liang SS *et al.* Protein-bound uremic toxins are associated with cognitive function among patients undergoing maintenance hemodialysis. *Sci Rep* 2019;**9**:20388. https://doi.org/10.1038/s41598-019-57004-7
113. Lin YT, Wu PH, Lee HH *et al.* Indole-3 acetic acid increased risk of impaired cognitive function in patients receiving hemodialysis. *Neurotoxicology* 2019;**73**:85–91. https://doi.org/10.1016/j.neuro.2019.02.019
114. Arund J, Tanner R, Uhlin F *et al.* Do only small uremic toxins, chromophores, contribute to the online dialysis dose monitoring by UV absorbance? *Toxins* 2012;**4**:849–61. https://doi.org/10.3390/toxins4100849
115. Arund J, Luman M, Uhlin F *et al.* Is fluorescence valid to monitor removal of protein bound uremic solutes in dialysis? *PLoS One* 2016;**11**:e0156541. https://doi.org/10.1371/journal.pone.0156541
116. Uhlin F, Fridolin I. *Optical online monitoring of uremic toxins beyond urea*. IntechOpen. https://doi.org/10.5772/intechopen.110080
117. Paats J, Adoberg A, Arund J *et al.* Optical method and biochemical source for the assessment of the middle-molecule uremic toxin β2-microglobulin in spent dialysate. *Toxins* 2021;**13**255. https://doi.org/10.3390/toxins13040255
118. Lauri K, Arund J, Holmar J *et al.* Removal of urea, β2-microglobulin, and indoxyl sulfate assessed by absorbance and fluorescence in the spent dialysate during hemodialysis. *ASAIO J* 2020;**66**:698–705. https://doi.org/10.1097/MAT.0000000000001058
119. Paats J, Adoberg A, Arund J *et al.* Time-averaged concentration estimation of uraemic toxins with different removal kinetics: a novel approach based on intradialytic spent dialysate measurements. *Clin Kidney J* 2022;**16**:735–44. https://doi.org/10.1093/ckj/sfac273
120. Zilliox LA, Chadrasekaran K, Kwan JY *et al.* Diabetes and cognitive impairment. *Curr Diab Rep* 2016;**16**:87. https://doi.org/10.1007/s11892-016-0775-x
121. Ling J, Ng JKC, Chan JCN *et al.* Use of continuous glucose monitoring in the assessment and management of patients with diabetes and chronic kidney disease. *Front Endocrinol* 2022;**13**:869899. https://doi.org/10.3389/fendo.2022.869899
122. Sugimoto T, Tokuda H, Miura H *et al.* Cross-sectional association of metrics derived from continuous glucose monitoring with cognitive performance in older adults with type 2 diabetes. *Diabetes Obes Metab* 2022;**25**:222–8. https://doi.org/10.1111/dom.14866

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