OXFORD

REVIEW

Care pathways for patients with cognitive impairment and chronic kidney disease

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ABSTRACT

Various epidemiological datasets and pathophysiological hypotheses have highlighted a significant link between chronic kidney disease (CKD) and cognitive impairment (CI); each condition can potentially exacerbate the other. Here, we review the mutual consequences of CKD and CI on health outcomes and care pathways and highlight the complexities due to the involvement of different specialists. Our narrative review covers (i) the burden of CI among patients with CKD, (ii) the impact of CI on kidney health, (iii) access to kidney replacement therapy for people with CI, (iv) resources in cognitive care and (v) potential models for integrated 'nephro-cognitive' care. CI (ranging from mild CI to dementia) has a significant impact on older adults, with a high prevalence and a strong association with CKD. Furthermore, CI complicates the management of CKD and leads to a higher mortality rate, poorer quality of life and higher healthcare costs. Due to difficulties in symptom description and poor adherence to medical guidelines, the presence of CI can delay the treatment of CKD. Access to care for patients with both CKD and CI is hindered by physical, cognitive and systemic barriers, resulting in less intensive, less timely care. Multidisciplinary approaches involving nephrologists, geriatricians, neurologists and other specialists are crucial. Integrated care models focused on person-centred approaches, shared decision-making and continuous co-management may improve outcomes. Future research should focus on the putative beneficial effects of these various strategies on both clinical and patient-reported outcomes.

Keywords: care access, care pathways, chronic kidney disease, cognitive impairment, co-management

INTRODUCTION

A link between chronic kidney disease (CKD) and cognitive impairment (CI) has been suggested by both epidemiological data and pathophysiological hypotheses. These two disorders not only influence each other but may also affect patients' care pathways, access to care and adverse outcomes. The presence of CI is likely to interfere with nephrological care, and the presence of CKD is likely to interfere with cognitive care, notably because the respective care pathways are operated by different specialist physicians and other health professional caregivers with differ-

ent backgrounds. Here, we review (i) the burden of CI among patients with CKD, (ii) the impact of CI on kidney health, (iii) access to kidney replacement therapy for patients who develop CI, (iv) the available resources and organization of care for people with CI and (v) potential models of 'nephrocognitive' care.

THE BURDEN OF CI IN PATIENTS WITH CKD

As a continuum running from mild CI (MCI) to major neurocognitive disorders (also referred to as 'dementia'), CI is a major risk

factor for poor health in the growing population of older adults worldwide. The prevalence of MCI among people aged 50 years and older is over 15% and more than the half of these individuals will develop major neurocognitive disorders (i.e. disorders with an impact on instrumental or basic activities) within 5 years. CI is associated with an increased mortality as compared with normal cognitive status [1]. Furthermore, dementia is the third-leading cause of death among older adults [2]. MCI and (especially) dementia reduce patients' quality of life (QoL) relative to healthy individuals [3].

Although CKD is not widely acknowledged as a major risk factor for dementia, it is strongly associated with CI. This phenomenon might be partly due to common risk factor profile. Cognitive changes may occur in the early-stage of CKD, and the severity of CKD is associated with the risk of developing CI: the lower the estimated glomerular filtration rate (eGFR), the higher the CI risk [4]. The Reasons for Geograhic and Racial Differences in Stroke study of adults in the USA found that each 10 mL/min/1.73 m^2 decrement in the eGFR below 60 mL/min/1.73 m^2 was associated with an 11% increment in the incidence of CI [5]. Patients with CKD often have comorbidities (and especially cardiovascular comorbidities) that may worsen treatment outcomes and health-related QoL. The presence of CI, along with cardiovascular diseases, contribute to lower life expectancy.

Haemodialysis (HD) patients have a 3-fold greater risk of developing severe CI than age-matched patients without CKD, and the estimated prevalence of CI among HD patients is 30%–40% [6]. In patients undergoing HD, a lower cognitive score (e.g. in the Mini Mental State Examination) is associated with greater technician time spent caring for patients after a dialysis session [7]. Delirium (reflecting cognitive vulnerability and decreased cognitive reserve), is associated with greater mortality in HD patients and kidney transplant (KT) recipients [8, 9]. The occurrence of an episode of delirium after KT is associated with a longer in-hospital length of stay, a higher mortality and a greater risk of being diagnosed with dementia [9, 10].

CI also has indirect consequences because it affects the life of patient's family members. Relative to caregivers of people without dementia, caregivers of people with dementia are significantly more stressed and have a greater risk of developing cardiovascular disease (especially hypertension), depression and anxiety [11]. Furthermore, both dementia and CKD have a negative impact on domestic and government budgets. The cost of living is 135% higher for people with dementia than for people without dementia. The net annual cost of dementia is at its highest 5 years after symptom onset. The costs of caring for patients with dementia and comorbidities are significantly higher than for patients with the same comorbidities but without dementia [12].

MUTUAL CONSEQUENCES OF CI AND CKD
The brain-to-kidney axis

Patients with CI may have difficulty adequately describing their symptoms; this increases the likelihood of undiagnosed or inadequately treated comorbid conditions, together with frequent additional comorbidities in this population. The presence of CI may therefore complicate or delay the management of comorbid conditions and have an adverse impact on them, increasing the risk of developing CKD [13]. Additionally, patients with CI may be unable to care for themselves and may have difficulty taking medications and adhering to dietary and medical recommendations.

Pathophysiological hypotheses linking CKD to cognitive dysfunction are numerous. Beyond the sharing of cardiovascular risk factors, CKD-related mechanisms may be involved such as the accumulation of uraemic toxins, the glymphatic system dysfunction, the disruption of blood–brain barrier or gut dysbiosis, arguing for both a vascular and a toxic hypothesis [14, 15]. Furthermore, some gut-derived uraemic toxins like indoxyl sulfate are known to exert an endothelial toxicity and to be associated with increased blood–brain barrier permeability [16]. In a recent cohort study including more than 300 000 individuals, episodes of acute kidney injury were associated with a higher risk of incident dementia [17]. In the other direction, there are few published data on the effects of brain health on kidney health. A large study conducted in Korea ($n = 558\,147$) observed an association between Alzheimer's disease (AD) or depressive symptoms and the risk of end-stage kidney disease (ESKD), supporting the hypothesis of a brain-to-kidney axis [18]. This concept has been proposed based on findings that acute brain injuries from trauma or stroke (ischaemic or haemorrhagic) coincide with frequent acute kidney injury [19]. Factors involved in such crosstalk remain only partially identified [20].

Assessment of kidney function during the aetiological work-up for CI

The assessment of kidney function is recommended during the aetiological work-up for CI. The serum creatinine concentration, eGFR and also albuminuria (or the urinary albumin to creatinine ratio) should be measured in all people displaying CI. Indeed, several studies reported that albuminuria might be a better predictor of impaired cognition than eGFR [21]. Moreover, the results of a Mendelian randomization study indicated that albuminuria was associated with decreased brain cortical thickness, which might reflect endothelial dysfunction in both the brain and the kidney [22].

Aetiological work-up for CI also includes clinical examination and brain imaging. Several imaging studies provide insights into the relationship between kidney function and brain health [15]. Most of them are cross sectional and observe structural but also functional differences between patients with CKD and healthy controls (Andrade *et al.*, *NDT* Supplement).

A recent development in the field of the diagnosis of AD is the use of blood biomarkers to predict dementia (Andrade *et al.*, *NDT* Supplement). In the MEMENTO cohort study which included 2323 non-demented patients, blood and cerebrospinal fluid concentrations of phosphorylated-tau (p-tau181) and neurofilament-light chain (NfL) similarly predicted AD dementia risk over a 5-year follow-up period, with no effect of the presence of CKD on prediction [23]. However, several recent studies have documented an association between CKD and the plasma level of p-tau181 and NfL [24]. In a large cohort ($n = 6256$) with 17 years of follow-up, impaired kidney function was associated with elevated plasma levels of NfL and p-tau181. Thus, kidney function might influence the predictive value of plasma biomarkers and should be considered during the diagnostic work-up for CI [25].

Access to care and referral to nephrologists for patients with CI

For people with CI, access to healthcare services is a multifaceted challenge, encompassing physical, cognitive and organizational barriers. Physical obstacles (such as transport difficulties) and consequences of CI (including deficits in memory, executive function, language, attention and processing speed) hinder effective

Table 1: Barriers and difficulties to healthcare access for patients with CI and/or CKD.

Direct consequences of cognitive impairment (memory, executive function, language, attention, …) and loss of autonomy	- Difficulties in realizing and describing adequately their symptoms - Complication and delay in management for comorbid conditions (including CKD) - Patient's difficulties in caring for themselves (medications, adhering dietary and medical recommendations) and making informed decisions (e.g. about KRT) - Physical obstacles and transport difficulties - Difficulty getting to consultation and care programs on one's own
Insufficient physicians training for caring patients with cognitive impairment	- Disparities in healthcare quality and outcomes with older adults with CI - Less guideline-concordant treatment for comorbid conditions for older people with CI - Confusion between MCI and dementia leading to less intensive care recommendations for older adults with CI
Gaps in healthcare program and system organization	- Limited screening programs for conditions linked to CKD (hyperlipidemia diabetes mellitus, breast and prostate cancer) - Disparities in healthcare access and robust welfare policies and universal healthcare - Increased health-related and non-health-related costs in patients with CI and/or CKD

navigation and utilization of the healthcare system [26]. These challenges extend to understanding medical needs and instructions, remembering to attend appointments and communicating with healthcare professionals. Moreover, healthcare providers' lack of training and expertise in caring for patients with CI leads to disparities in healthcare quality and outcomes with older adults with CI receiving less guideline-concordant treatment for comorbid conditions [27]. Additionally, the confusion between MCI and dementia by physicians often results in less intensive care recommendations for older adults with CI [28]. Social policies also play a significant role in healthcare access; not all countries have robust welfare policies and universal healthcare. Together, these barriers contribute to pronounced disparities in healthcare access and quality for this vulnerable population (Table 1).

Although nephrological resources are limited in some care systems, nephrologists should be involved in the multidisciplinary management of patients with CI. People displaying significant impairment in kidney function (i.e. an eGFR <30 mL/min/1.73 m^2), abnormal albuminuria and/or haematuria, CKD progression or resistant hypertension should be referred to a nephrologist as soon as possible. This early referral allows for the implementation of nephroprotective medication to slow down the decline in kidney function, and eventually to discuss and prepare for the most suitable kidney replacement therapy (KRT) [29]. However, a survey found that primary care providers in the USA were less likely to refer older patients with stage 4 CKD to a nephrologist when they displayed moderate dementia [30].

Although most of the cost per patient in the CKD population is related to ESKD, earlier stages of CKD also generate costs, mainly by inducing cardiovascular events and associated hospitalizations. Per patient healthcare cost is estimated to double in patients with CKD as compared with patients without CKD. Non-healthcare-related costs (loss of productivity, costs related to informal caregivers…) are probably underestimated especially in patients receiving renal replacement therapy [31].

ACCESS TO KRT IN COGNITIVELY IMPAIRED PATIENTS

There are two main concerns with regard to KRT in cognitively impaired patients with advanced CKD: how CI influences access to KRT in general, and whether there is a preferred KRT modality for patients with CI.

**Table 2:** Tools to improve treatment modality choice in ESKD and CI.

Propose an advanced care planning
Evaluate the risk of incident kidney failure (KFRE)
Define patient's preference as soon as possible and regularly
Involve caregiver in discussion (after patient agreement)
Propose the use of decision aid tools
Screen for CI (cognitive screening tests)
Refer the patient for a comprehensive and multidisciplinary assessment (including geriatric expertise when appropriate)
Complete the aetiological work-up in case of CI, involving neuropsychologist, neurologist or geriatrician

KFRE, Kidney Failure Risk Equation.

CI and access to KRT

On one hand, cognitively impaired patients with CKD may be denied access to care due to limited referrals by healthcare providers who judge that they may not benefit from further treatment. On the other hand, CI can compromise a person's ability to care for themselves or to make informed decisions (e.g. about KRT). Interestingly, a patient's self-perceived cognitive incapacity may limit their choice of a self-care dialysis modality [32]. CI seems associated with a lower likelihood of peritoneal dialysis (PD) as the first dialysis modality [33]. Support from relatives is crucial and must be carefully evaluated. When a patient is unable to choose, the decision often involves a surrogate (family member or healthcare professional), representing a difficult and stressful option, especially when the patient's wishes are not known. To avoid this scenario and to identify the patient's values, preferences and goals, advanced care planning should be initiated as soon as possible (Table 2). The use of a formula, such as Kidney Failure Risk Equation to estimate a 5-year kidney failure risk, may be useful to estimate needs, to define the time frame and to prioritize actions [34].

Decision aids (DAs) may be also useful in this respect because they can (i) help patients to make their decisions explicit, (ii) provide information about options and associated benefits/harms, and (iii) clarify congruence between decisions and personal values [35]. Along with non-specific DAs, several open-access ESKD-specific tools (mostly in English) have been developed. Patient associations are also active in highlighting patients' decision needs and providing documents in the local language. A randomized controlled trial showed a reduction of decisional conflict for
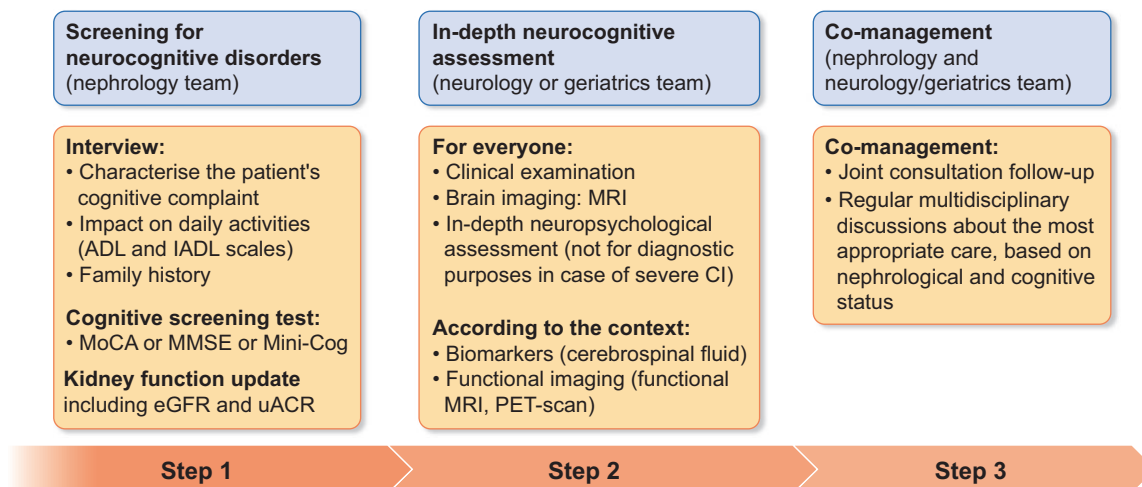
ADL, activities of daily living; IADL, instrumental activities of daily living; CI, cognitive impairment; MoCA, Montreal Cognitive Assessment; eGFR, estimated glomerular filtration rate; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; PET, positron emission tomography; uACR, urinary albumin creatinin ratio

Figure 1: Proposed steps for the care management of patients with CKD undergoing CI.

renal therapy in patients from 70 years and older with CKD stages 4 to 5, with the use of DAs [36].

To provide appropriate, personalized opportunities for KRT, all patients with advanced CKD (and especially older or frail patients) should undergo a comprehensive assessment that includes screening for CI. The main objectives of this assessment are: to (i) diagnose potentially reversible causes of impairment (such as depression) and intervene in a timely way; (ii) define the patient's baseline level of functioning; (iii) start advanced care planning before the patient loses the ability to express their preferences and choose a KRT; and (iv) determine whether CI is a potential complication of CKD or of another neurodegenerative disorder (such as AD and vascular dementia). In that sense, it would be wise to define a screening strategy covering the choice of cognitive screening test (for example, a brief tool like Mini-cog or Montreal Cognitive Assessment (MoCA) and the frequency of administration (annually, for example) [37]. It is noteworthy that decisional autonomy (i.e. a patient's ability to take decisions) cannot be predicted solely from the results of cognitive assessment [38].

Choice of the KRT modality

The initiation of dialysis may reverse some of the mechanisms that contribute to cognitive decline (through the removal of uraemic toxins, and the correction of hyperparathyroidism and fluid overload) and may thus lead to a small improvement in overall functional status [39]. However, dialysis has also been linked to an elevated risk of CI due to intradialytic changes in blood pressure and their consequences on cerebral blood flow [40].

The literature data on the best KRT modality for patients with CI are contradictory. Firstly, although it is generally accepted that kidney transplantation may maintain or even improve cognition (relative to dialysis), this improvement appears to be smaller in frail patients [41]. Moreover, the immunosuppression required by KT recipients can affect long-term cognition [42]. Additionally, patients with CI are less likely to be placed on the waiting list for KT and are more likely to die while on the list [43]. Good long-term adherence to immunosuppressive treatment (affected by the presence of CI) and the risk of post-transplantation pro-

gression of CI are crucial considerations in any pre-transplant assessment.

Secondly, several studies observed that all dialysis modalities are associated with an elevated risk of incident dementia [44]. Some experts suggest that there are no differences between dialysis modalities [45], whereas others tend to favour PD over HD—especially for patients who receive a sufficient support from their relatives [46]. Studies advocating for the same risk for both dialysis modalities suggest that differences may reflect a selection bias of the initial modality selection, particularly for younger and more robust patients for PD [47]. Studies that highlight differences between PD and HD emphasize the importance of residual renal function for maintaining preserved cognition [48]. The optimal frequency of HD, total time on HD, ultrafiltration volume and dialysate temperature are also subject to debate [49]. HD modalities that leads to reduced haemodynamic changes such as nocturnal long session HD along with individualized modalities (home-based HD, incremental or decremental approach) may be preferable for patients with CI or at high risk of CI [50]. There is no clear evidence to recommend the choice of HD rather than PD and vice versa, especially in the absence of randomized controlled studies [51].

Thirdly, comprehensive conservative care is another treatment option in ESKD, it combines the usual treatments for CKD (except replacement therapy) with holistic patient-centred care and palliative care approach [52]. This alternative represents a legitimate option for frail and older patients for whom dialysis may not extend life and/or improve QoL, but it is rarely proposed by nephrologists [53]. In a study of barriers to conservative treatment, researchers did not observe a difference in cognitive performance between patients who were informed about conservative treatment options and those who were not [54].

RESOURCES AND ORGANIZATION OF CARE FOR PATIENTS WHO DEVELOP CI

From diagnosis to post-diagnosis care and support, today's care pathways for patients with CI are typically complex and non-
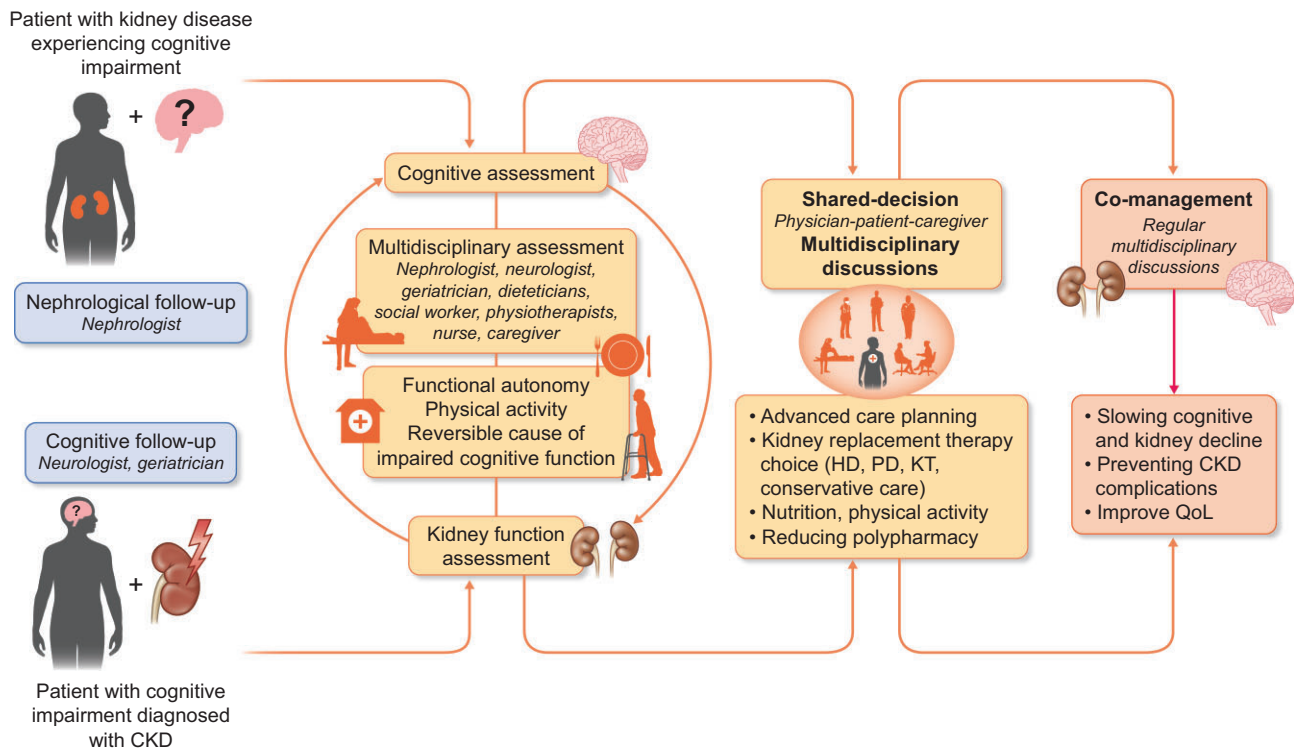
Figure 2: Care pathways for patients with CKD who develop cognitive impairment and for cognitively impaired patients with CKD: a call for multidisciplinarity and co-management.

standardized [55]. For people with CI, primary care physicians are often the first point of contact with the healthcare system. However evidence shows that the diagnosis of dementia is often inadequate in general practice, particularly at early stages, and with greater delays observed among individuals from racial and ethnic minority groups [56]. There are also documented shortcomings among other healthcare specialists (e.g. neurologists and geriatricians) involved in CI screening, detection and/or aetiological diagnosis; this leads to further delays in accessing appropriate medical care, financial and legal planning, and obtaining services and support [57].

Older adults with CI are heavy users of healthcare services: they have high comorbidity burdens and challenging care needs, and may become dependent on assistance in activities of everyday living [58]. People with AD or a related dementia have a high risk of long hospital stays, frequent visits to the emergency department, and home care affected AD or related dementias have a high risk of extended hospitalizations, frequent visits to the emergency department and home healthcare [57].

In the same way that patients with CI have limited or complicated access to care, access to non-nephrological care is often difficult among patients with CKD receiving conservative care or dialysis therapy. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend the administration of psychological assessment in selected categories of patients with CKD, such as KT candidates [59]. However, these guidelines do not explicitly cover cognitive issues following such assessment. As discussed earlier, there is a need for multifaceted assessment (i.e. including both clinical/medical and psychosocial factors) of all candidates for KT [60]. Furthermore, KT recipients require psychological assessment and support post-transplantation. Some governments strongly recommend or require the provision of psychological assistance to patients with CKD undergoing dialysis or transplantation [61]. A study in the UK observed considerable

centre-to-centre variability in approaches to identifying and treating depression in patients with CKD; indeed, a few kidney centres reported that they did not provide any psychosocial support, highlighting potential inequities in accessing psychosocial care for these patients [62]. To the best of our knowledge, there are no published specific data on access to cognitive care for patients with CKD.

Nephrology team can play a key role in the awareness of CI in patients with CKD in being attentive to patients and caregivers' complaint, assessing physical activity and functional ability in daily life and administering cognitive screening tests (Fig. 1).

POTENTIAL MODELS OF 'NEPHRO-COGNITIVE' CARE MANAGEMENT

The presence of neurocognitive disorders in patients with CKD induces complexity and requires coordination between several specialists. In the management of these patients, the key challenges are to avoid (i) the aggravation of neurocognitive disorders by CKD, (ii) the aggravation of CKD by neurocognitive disorders, and (iii) synergistic negative effects on outcomes such as loss of functional autonomy. As a result, CKD needs to be placed regarding to the patient's sociomedical context, life project and ability to adhere to treatment.

Multidisciplinary care is crucial in managing these patients and requires coordinated intervention by all the stakeholders in the care process: nephrologists, cardiologists, geriatricians, neurologists, dieticians, physiotherapists, social workers, nurses, caregivers, family members, etc. This coordination enables the transition from a disease-centred approach to a person-centred approach in which the patient is the centre of the decision-making process and can express their own wishes—even when neurocognitive disorders are present [63]. It also favours the implementation of shared medical decision-making via exchange of

information and treatment preferences between caregivers on one hand and the patient and their family on the other. These approaches are known to be associated with positive outcomes [64]. Shared decision-making and multidisciplinarity also facilitate optimal nutrition, the prevention of CKD-related complications, a reduction in polypharmacy through deprescribing and the introduction of physical activity (to help slow the decline in renal and cognitive functions over time) in patients with CKD [65, 66].

Many studies have demonstrated the benefits of multidisciplinary assessment in managing older patients, in whom neurocognitive disorders are more common [67]. However, most studies addressed the assessment of frailty (with cognition as part of the discussion), and few evaluated the effects of combining nephrology and geriatric care on life expectancy and QoL.

Several co-management models involving geriatricians and other specialists (surgeons for perioperative situations, oncologists for cancer care, etc.) are known to reduce mortality and morbidity in older adults [68]. Cognition is a dynamic process influenced by many factors (e.g. patient characteristics, clinical variables, comorbidities and treatment), and CKD is a progressive disease. Consequently, a multidisciplinary initial assessment is important for developing a personalized treatment strategy but must be followed by long-lasting collaboration between the nephrologist and the neurologist or geriatrician.

Although a model for 'nephrocognitive care' has not yet been validated, joint monitoring during consultations and regular multidisciplinary discussions would enable the various problems encountered by the patient to be discussed and tackled [69] (Fig. 2). These discussions might also facilitate optimal, shared decisions to be taken with regard to the choice of KRT and any associated adaptations: pre-habilitation for KT candidates, progressive dialysis, and better coordination between conservative care and supportive care. This type of management model requires care coordination and regular monitoring, in which a nurse trained in both nephrology and geriatrics/cognitive care has a key role in alerting specialists to any changes in disease trajectories and thus enabling treatments to be adjusted [70].

CONCLUSION

The interrelationships between kidney function and cognitive function have significant consequences for patients, caregivers, physicians and the healthcare system. Patients with both CKD and cognitive decline are likely to encounter difficulties in accessing optimal care. Even though resources are not extensive, various tools could be implemented to improve the quality of care in practice: opportunistic cognitive screening for patients with CKD, regular kidney function assessments (eGFR, albuminuria) for patients with CI, comprehensive multidisciplinary assessments, shared decision-making and co-management. Future research should focus on the putative beneficial effects of these various strategies on both clinical and patient-reported outcomes.

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DATA AVAILABILITY STATEMENT

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

CONFLICT OF INTEREST STATEMENT

Authors do not have any conflict of interest relating with this manuscript. The results presented in this paper have not been published previously in whole or part, except in abstract format.

APPENDIX
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