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Cognitive Impairment and Kidney Transplantation: Underestimated, Underrecognized but Clinically Relevant Problem

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Keywords

Cognitive dysfunction · Immunosuppression · Kidney transplantation

Abstract

Background: Chronic kidney disease (CKD) affects the cross-talk between organs in the body and vast majority of studies were devoted to the interactions between the kidneys and the cardiovascular system. As of today, there is more evidence of the kidney and the central nervous system connections. ***Summary:*** Indeed, CKD and in particular dialysis therapy is linked to the increased prevalence of neurological complications, such as cerebrovascular disorders, movement disorders, cognitive impairment, and depression. Both traditional cardiovascular risk factors (such as diabetes, hypertension, and lipid disorders), nontraditional risk factors (such as uremic toxins, anemia, and secondary hyperparathyroidism) may predispose CKD patients to neurological disorders. Likewise, cognitive problems occur more commonly in kidney transplant recipients, regardless of age, than in the general population, but the prevalence is still understudied. Cognitive impairment is associated with a higher risk of hospitalization, mortality, decreased quality of life, or health care costs in kidney transplant recipients. Here, we review (i) the potential clinical impact of kidney transplantation on cerebrovascular and neurological complications, (ii) evaluation of patients with cognitive impairment for kidney transplantation (iii) the potential impact of cognitive impairment on waitlisted and transplanted patients on patient care, and (iv) unmet medical needs. ***Key Messages:*** Cognitive impairment in kidney transplant recipients is an underestimated, underrecognized but clinically relevant problem. The screening for cognitive declines after kidney transplantation is not yet a routine practice. Several prospective and cross-sectional studies reported improvement across some of the assessed cognitive domains after transplantation.

Introduction

Cognitive impairment is defined as a decline in at least two out of several domains of cognitive function [1]. That might be deterioration in executive function (e.g., planning, reasoning, flexible thinking), concentration-attention/abstract thinking, general cognitive status, information and motor speed, spatial reasoning, language, verbal fluency, verbal memory, and visual memory [1–3]. There is not one standard neuropsychological test, so different tests battery are used across studies. Mini-Mental State

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Examination and Montreal Cognitive Assessment (MoCA) are widely used screening tools for mild cognitive impairment [4, 5]. Mini-Mental State Examination might not be sensitive enough to detect subtle cognitive deficits, while MoCA is validated and more precise with a sensitivity of 80%–100% and specificity of 50%–76% with a cut-off score of 25/26 [3–5]. MoCA consists of a one-page test with maximum point of 30 and assesses all domains of cognition [5].

Cognitive Impairment in Chronic Kidney Disease

It is well known that all stages of chronic kidney disease (CKD) are an independent risk factor for cognitive impairment, but there is no single mechanism responsible for cognitive decline [6–8]. Different possible causes that lead to vascular damage or endothelial dysfunction are being taken into account, which in turn may impact cognitive processes [8–10]. It was proved that uremic toxins, like elevated homocysteine levels, cystatin-C, and guanidine compounds influence the development of cerebral vascular diseases [8, 9, 11]. Otherwise, traditional risk factors such as ageing, comorbid disease, i.e., hypertension, diabetes mellitus, hypercholesterolemia, and nontraditional risk factors, i.e., chronic inflammation, oxidative stress, hypercoagulable state should also be taken into consideration [1, 8, 12]. Additionally, many studies reported that magnetic resonance imaging (MRI) of the brain in CKD patients, also young patients, show subclinical brain lesions like white matter hyperintensities, silent lacunar infarcts, microbleeds, and cerebral atrophy [13–15]. The prevalence of cognitive impairment in end-stage renal disease patients has been estimated at 50%–80% [16, 17].

Cognitive Impairment in Kidney Transplant Recipients

Kidney transplantation (KT) is the treatment of choice for patients with end-stage renal disease but is limited by the scarcity of organs available for transplantation. Frailty, a biologic syndrome of decreased reserve and resistance to stressors, is reflective of global health status and is emerging as an important prognostic marker in surgical and transplanted patients [18–20]. In addition, frailty measured at the time of transplantation was associated with a 94% increased risk of delayed graft function and a 61% increased risk of re-hospitalization in kidney transplant recipients [21, 22]. As frailty is most typically conceptualized as a physical syndrome, subjects with CKD may also be more vulnerable to health stressors if they are cognitively impaired. Executive function – the ability to pay attention, plan, and organize – is the cognitive domain affected most often.

Recent studies started to focus on the potential effects of cognitive deficits on patients facing initiation of dialysis therapy or managing complex drug regimens [23, 24]. It has been shown that cognitive impairment was associated with higher venous catheter use at dialysis initiation [25] and greater risks of all-cause graft loss after kidney transplantation [26].

Intact cognition is generally a prerequisite for navigating through and completing evaluation for kidney transplantation. Despite the fact that severe dementia is a contraindication for kidney transplantation, screening for more mild forms of cognitive impairment before referral is seldom. Kidney transplant candidates may have unrecognized cognitive impairment, which may prolong evaluation, enhance mortality risk, and hinder access to kidney transplantation. Michelson et al. [27] assessed the prognostic utility of "timed up and go test" – TUGT and its associations with waitlist and posttransplant outcomes for kidney transplant candidates. They reported that transplanted individuals had shorter TUGT times than those who remained on the waitlist (8.99 vs. 9.79 s, $p < 0.001$). They concluded, that after adjusting for age, the TUGT performed at the time of the evaluation was not associated with short-term outcomes including waitlist removal and length of stay following transplantation. They found that MoCA test results were not associated with kidney transplant waitlist outcomes; however, passing the TUGT was associated with receiving RT or remaining on the list.

Bozhilo et al. [28] in the retrospective study examined 526 KT candidates. They underwent TUGT and MoCA (2015–2019) and were divided into "favorable" (transplanted or remained on the list) or "unfavorable" (not listed, removed from list, or died) outcomes.

Ng et al. [29] performed a retrospective review of our pre-KT patients, who consist mainly of Hispanics and Native Americans, over a 16 months period. They collected data on baseline demographics and MoCA scores, at the initial KT evaluation and defined cognitive impairment as MoCA scores of <24. In their study, 154 patients completed the MoCA during their initial evaluation with mean (standard deviation) MoCA scores of 23.9 (4.6), and 58 (38%) participants with scores <24. Advanced age, lower education, and being on dialysis were associated with lower MoCA scores. They concluded that cognitive impairment was common in our pre-KT patients and was associated with a lower likelihood of KT wait-listing.

Gupta et al. [23] examined whether cognitive impairment influences the likelihood for transplant listing and whether patients with cognitive impairment take longer to be listed. They considered a score <26 as indicated cognitive impairment. Among 349 patients who underwent MoCA testing at their initial visit, cognitive impairment with MoCA < 26 was diagnosed in 193 patients (55%). Patients with cognitive impairment were more likely to be older, black, and smokers. Cognitive impairment was independently associated with a lower likelihood of being listed for transplant (hazard ratio, 0.93 per unit lower MoCA score; 95% confidence interval, 0.88–0.99; p = 0.02). They also concluded that cognitive impairment was associated with longer time to be waitlisted for transplantation.

Chu et al. [24] studied 3,630 participants (January 2009 to June 2018) with cognitive function measured by the Modified Mini-Mental State Examination (3MS) evaluated for possible kidney transplantation. They found that at evaluation, 6.4% of participants had cognitive impairment, which was independently associated with 25% lower chance of listing (adjusted HR, 0.75; 95% CI, 0.61–0.91). They also conclude that cognitive impairment in patients without diabetes was associated with increased mortality on the waitlist. Table 1 shows studies on cognitive functions in kidney transplant recipients.

Moreover, cognitive problems occur more commonly in kidney transplant recipients, regardless of age, than in the general population, but the prevalence is still understudied [30, 31]. Cognitive impairment is associated with a higher risk of hospitalization, mortality, decreased quality of life, or health care costs [30, 32]. The screening for cognitive declines after kidney transplantation is not yet a routine practice [3]. On the other hand, several prospective and cross-sectional studies reported improvement across some of the assessed cognitive domains in kidney transplant recipients [2, 30–38]. Thomas et al. [26] using the 3MS examination, measured global cognitive function at KT hospital admission in a prospective, 2-center cohort of 864 KT candidates (August 2009 to July 2016). In living donor KT recipients, the prevalence was 3.3% for mild impairment ($60 \leq 3MS < 80$) and 3.3% for severe impairment (3MS < 60). In deceased donor KT recipients, the prevalence was 9.8% for mild impairment and 2.6% for severe impairment. They also found that kidney recipients both from living and deceased donors with cognitive impairment had substantially higher all-cause graft loss risk than unimpaired recipients. Anwar et al. [39] showed significant differences in cognitive function test results between transplant and hemodialysis patients ($p < 0.01$), suggesting that transplant patients were superior in their cognitive performance, with the correction of anemia being the most important factor for improving cognitive performance in both groups. There were no significant differences between transplant patients and control subjects in psychometric measures ($p > 0.05$).

Griva et al. [33] showed significant improvements regarding verbal and non-verbal memory after kidney transplantation. There were no changes in measures of other cognitive domains: attention, visual planning, mental processing speed, and motor abilities. Additionally, older kidney transplant recipients and patients with longer time dialysis prior transplantation showed less improvement. Harciarek et al. [34] compared kidney transplant recipients' mean age of 46 before and after transplantation – with age-matched nontransplanted patients and with healthy controls. Cognitive functions were analyzed prospectively three times over the time of the study, the last time – 1 year after a successful kidney transplant. Patients after successful kidney transplant gained statistically significant improvement in performance on the tests of motor/psychomotor speed, visual planning, memory, and abstract reasoning not only right after surgery but also 1 year after. On the other hand, in dialyzed patients, verbal memory declined over the time of the study [2]. Meta-analysis based on 10 articles has found improvement regarding general cognitive status performance as well as several cognitive domains after kidney transplantation. Transplanted patients reached better results in the domains of information and motor speed, spatial reasoning, verbal and visual memory as compared to dialysis period, and this improvement was still preserved in the follow-up period 1 or 2 years after. However, there were no differences in the three cognitive domains, i.e., executive function, verbal fluency and language before and after kidney transplantation and between transplanted and nontransplanted patients. What is more, these subjects had lower test results than healthy controls [2]. Van Sandwijk et al. [35] analyzed cognitive function and combine this with the results of brain MRI of kidney recipients before and 1 year after transplantation. One year after a successful kidney transplant, the patients improved at tests assessing working memory. Furthermore, these improvements were significantly correlated with increase in the volume of white matter and *N*-acetylaspartate/creatine ratio, which is a marker for neuronal integrity [35]. There have been far fewer studies assessing the long-term effects of kidney

Table 1. Summary of studies evaluating cognitive functions in kidney transplant recipients

Study	Design	Sample/age, years	Results
Pflugard et al. [15]	Cross-sectional observational, kidney transplant patients compared with kidney transplant patients, liver transplant patients, and healthy controls	21 patients 10 years after kidney transplantation/55.9±10.3 10 patients 5 years after kidney transplantation/56.7±6.5 11 patients 1 year after kidney transplantation/54.4±4.5 9 patients after liver transplantation/50.3±11.4 17 healthy controls/56.8±8.2	Impaired cognitive function in kidney and liver transplant patients Presence of pathological changes in brain MRI 1 and 5 years after kidney transplantation Reduced brain metabolism after kidney transplantation
Griva et al. [33]	Prospective longitudinal study, pre-transplant dialysis patients were assessed before and after transplantation	28 transplant patients/44.04±12.01	Improvements in verbal and nonverbal memory after kidney transplantation
Harciarek et al. [34]	Prospective longitudinal study, pre-transplant dialysis patients were assessed after transplantation compared with dialysis patients and healthy controls	27 kidney transplant patients/46.1±10.9 (previously on HD: 17, PD: 10) 18 dialyzed patients/44.9±11.8 (HD: 12, PD: 6) 30 controls/47.23±10.2	Improvements in performance on tests of motor/psychomotor speed, visual planning, memory, abstract reasoning 1 year after transplantation
Van Sandwijk et al. [35]	Prospective observational cohort study, transplant recipients and donors	27 recipients/53±13 24 donors/55±13	Improvements in working memory, increase in the volume of white matter, and *N*-acetylaspartate/creatine ratio 1 year after kidney transplantation
Gelb et al. [36]	Cross-sectional study, transplant patients were compared with CKD patients and healthy controls	42 kidney transplant patients/55.24±10.96 45 predialysis CKD patients/59.67±11.88 49 healthy controls/57±13.59	Impaired verbal memory and executive function in kidney transplant patients and CKD patients
Troen et al. [37]	Cross-sectional, transplant patients compared with norms	183 transplant patients/54±9.5	Impaired executive function, memory, attention, and mental processing speed after kidney transplantation

transplantation on cognition. Recently, Pflugrad et al. [15] investigated cognitive function, brain structure, and metabolism in patients treated by standard-dose tacrolimus therapy 10 years after kidney transplantation. The control group consisted of kidney recipients 1 and 5 years after successful surgery, tacrolimus treated patients after liver transplantation and healthy controls. In the long term, cognitive impairments were present in all patients after kidney and liver transplantation as compared to healthy controls, mainly in visuospatial/constructional domains. Furthermore, MRI brain images displayed much more periventricular and white matter hyperintensities in patients 1 and 5 years after surgery as compared to healthy controls, but this difference was not still statistically significant after 10 years. Additionally, researchers found significantly reduced brain adenosine triphosphate concentrations and, in consequence, reduced brain metabolism in patients after kidney but not liver transplantation (patients also received tacrolimus) as compared to healthy controls. These results indicate that many years after kidney transplantation cognitive problems may reoccur in recipients and tacrolimus therapy alone is not sufficient to lead to cognitive decline and altered brain energy metabolism in kidney recipients [15]. Two other studies investigated cognitive function outcomes approximately 5 and 7 years after successful kidney transplantation [36, 37]. In both studies, kidney recipients revealed cognitive impairment, e.g., in the domains of memory and executive function in the long term after transplantation. Moreover, 30% of patients showed symptoms of mild to severe depression [37].

Drug and Nondrug Approaches to the Treatment of Cognitive Disorders

There is no effective treatment that has been approved by regulatory agencies to slow or prevent cognitive impairment in kidney transplant recipients. Cholinesterase inhibitors, i.e., donepezil, galantamine, and rivastigmine or *N*-methyl-D-aspartate receptor antagonists, i.e., memantine are commonly used to temporarily reduce cognitive symptoms in Alzheimer's disease but are not recommended (except rivastigmine) to treat other diseases. That is why it is important to identify and treat possible modifiable risk factors, i.e., anemia or vascular risk factors [40]. Additionally, it was proved that physical activity has a positive effect on cognitive improvement in general population [41]. According to the review written by Calella et al. [42] physical training after kidney transplantation improved cardiorespiratory efficiency, muscle strength, and quality of life. Additionally, some studies showed that exercise training reduces anxiety or depression [43] and an increase of the sleep quality and quantity [44].

The Potential Impact of Immunosuppressants on Cognitive Function

Immunosuppressive drugs might affect the cognitive functions. Tree drugs, cyclosporine, tacrolimus, and sirolimus are commonly used. They all block interleukin-2 (IL-2) production. Tacrolimus and cyclosporine inhibit the action of the phosphatase calcineurin and in a consequence prevent the transcription of mRNAs for cytokines, such as IL-2 [45] and sirolimus blocks the signal transmission of IL-2 receptors [46]. Martinez-Sanchis et al. [47] showed that subjects treated with tacrolimus and sirolimus had worse results in tests assessing attention and working memory as compared with cyclosporine and the control group. In addition, tacrolimus and sirolimus, but not cyclosporine, impair the performance of patients [47].

The Potential Impact of Cognitive Impairment on Waitlisted and Transplanted Patients on Patient Care

Patients with cognitive impairment might have been judged at greater risk of medication nonadherence, which is of utmost importance in kidney transplant recipients. In addition, frail or cognitively impaired patients may have worse outcomes that would imperil evaluation for organ transplantation or may lead to too many costly complications, such as intensive care or long hospitalizations. On the other hand, Basu et al. [48] stressed that transplant evaluation may be too complex and challenging for frail and cognitively impaired patients to navigate successfully. However, we should bear in mind that as shown by Reese et al. [49] patients with limited functional status live longer with transplant compared with dialysis, and it is likely that many patients with frailty and cognitive impairment would also live longer if transplanted. Moreover, in cognitively impaired patients with nonadherence, strong social support may overcome the problem. We also have to take into account that some frail or cognitively impaired patients may not be taken seriously as transplant candidates during evaluation process. Up to date frailty and cognitive impairment are not included in current risk adjustment algorithms for waiting list and transplant outcomes. In the situation when organs for transplantation are rare and precious resource, questions about how to best use them are extremely valid from a public health perspective due to the known associations between frailty, cognitive impairment, and graft loss. On the other hand, we need to consider the fact that successful kidney transplantation is associated with substantial improvement in cognitive but the magnitude and likelihood of sustained improvement is in some cases difficult to predict.

From the practical perspective, every patient evaluated as a potential kidney transplant recipient should be also evaluated for the presence of cognitive impairment. Cognitive impairment in elderly patients either with CKD or following kidney transplantation could be prevented by controlling blood pressure or the use of anticoagulation in patients with atrial fibrillation, which is particularly frequent in patients with CKD, in order to prevent cerebrovascular lesions (always take into account the interactions with immunosuppression). If a potential kidney transplant recipient is mildly or moderately cognitively impaired on a screening test, more detailed neurocognitive testing should be considered. Further evaluation, based on a framework suggested for addressing cognitive impairment in the general population, may include referral to either a geriatrician or a neurologist. In this case, nephrological care could also influence the occurrence of neurological complications. Imaging studies using either computed tomography or MRI should be performed in any case with focal deficits, rapid decline, or recent trauma and should also be taken into account in subjects with cognitive impairment of unclear cause. Finally, screening for reversible causes of cognitive impairment, such as vitamin B_{12} deficiency or thyroid dysfunction should be performed as tests for these conditions are simple and noncostly. We should also take into account that anticholinesterasic drugs and memantine should be used with caution in patients with CKD because most of these drugs accumulate in case of low glomerular filtration rate. In addition, optimization of traditional CVD risk factors, avoidance of sedating drugs and polypharmacy, improvement of sleep hygiene, better family and social support, depression therapy, and mental stimulation and exercise encouragement [50–54] are also should be implemented. For improvement of treatment adherence, several measures should be introduced as drugs management plans, frequent check-ins, use of clear written instructions, and close involvement of social workers, dieticians, technicians, nurses, and physicians to yield the best possible outcomes.

Unmet Needs

In the course of a CKD, cognitive impairment is becoming a growing health problem. There are limited data investigating the incidence of cognitive impairment in renal transplant recipients. In addition, there are no formally validated screening tests for either CKD patients or kidney transplant recipients. Recently, many scientists have found improvements in several cognitive domains in patients after a successful kidney transplant, but recovery has not been complete and long-lasting. For the most part, the studies presented so far were based on the short-time observation. Unfortunately, the interpretation of study data is difficult because of different study designs and small sample sizes. There were only a few prospective longitudinal studies, most studies were cross-sectional. In addition, immunosuppressive therapies, i.e., tacrolimus might have an adverse impact on cognitive function. Moreover, nearly a third of transplanted patients suffer from depression [46]. Thus, depressive symptoms might affect attention, memory, and executive function or weaken the final result in cognitive testing. Only in some studies, the results were adjusted for symptoms of depression [15, 33, 35]. In addition, there is a notable lack of specific treatments available. This may in part be due to exclusion of CKD patients from clinical trials in the general population and may also reflect the multiple different contributors to CKD-related cognitive impairment. There are no data available from clinical trials for kidney transplant recipients, we can only extrapolate the data from general population taking into account many biases. As our dialyzed population is getting older, we have more problems also in our transplanted patients. Therefore, further research is needed to understand epidemiology, course, and consequences of cognitive difficulties in patients who have undergone renal transplantation and effect of immunosuppression as well as to test novel strategies to prevent or limit cognitive decline.

Conclusions

Cognitive impairment is relatively common in transplanted patients and associated with a higher risk of hospitalization, mortality, decreased quality of life, or health care costs. Several studies reported improvement across some of the assessed cognitive domains after transplantation. However, the screening for cognitive declines after kidney transplantation is not yet a routine practice. As our kidney transplant recipients are getting older and more frail, assessment of cognitive function should be considered to introduce appropriate therapy timely and efficiently.

Conflict of Interest Statement

Authors declare no conflict of interests.

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Author Contributions

A.G. and J.M.: conception of the study; A.G., J.S.M., and J.M.: writing the manuscript; J.M.: critical revision.

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