Exploring Cognitive Dysfunction as a Secondary Effect of Kidney Disease: Unveiling the Kidney-Brain Interconnection. A Literature Review

Dr. Sc. (c) Vilma ÇADRI
Department of Nephrology, University Hospital Center "Mother Teresa", Tirana, Albania
Corresponding Author
vilma.cadri@gmail.com

Prof. Asoc. Dr. Ariana STRAKOSHA
Department of Nephrology, University Hospital Center "Mother Teresa", Tirana, Albania

Dr. Sc. Nevi PASKO
Department of Nephrology, University Hospital Center "Mother Teresa", Tirana, Albania

Dr. Sc. Elvana RISTA
Department of Nephrology, Hygeia Hospital, Tirana, Albania

Abstract

***Background**: Chronic Kidney Disease (CKD) is increasingly recognized as a systemic condition affecting not only renal function but also various extra-renal systems, including the central nervous system. Cognitive impairment (CI) has emerged as a*

significant concern in CKD patients, manifesting as a spectrum ranging from mild cognitive deficits to clinically relevant dementia.

***Methods**: A literature research of electronic databases (Pub-med library, NDT articles and Google Scholar covering the period from 2003-to March 2024) were conducted to assess the association of CKD and cognitive impairment. **Results**: This literature review explores the historical perspectives, definitions, clinical significance, methodological challenges, and potential mechanisms underlying CI in CKD. Furthermore, it highlights ongoing research initiatives, structural and hemodynamic similarities between the kidney and brain. **Conclusions:** Increasing clinician's awareness of CI in CKD is essential to improving its early identification. Therefore, the early identification of possible precursors of CI and the diagnosis and prevention of it is of increased importance. Due to the complexity of CKD, there is tremendous need for increased multidisciplinary team for future directions in this ever-expanding area which is pivotal to our patient's quality and quantity of life.*

Keywords: Cognitive impairment, chronic kidney disease, kidney-brain axis

Introduction

In recent years, the complex interplay between kidney dysfunction and cognitive decline has emerged as a focus of attention in research and clinical interest. Chronic Kidney Disease (CKD), a systemic condition characterized by progressive loss of renal function, has an increasing recognition not only affecting the kidneys but also a decisive impact on extra-renal systems, including the central nervous system (CNS)[1]. Among the diverse of neurological complications

associated with CKD, cognitive impairment (CI) is most prominent which is accompanied by symptoms such as depression and sleep disturbances. CI encompasses a spectrum of cognitive deficits ranging from mild impairment to clinically relevant dementia[2].

The connection between kidney dysfunction and cognitive decline has been underexplored, specifically focusing on renal outcomes. However, increasing evidences have highlighted the interconnection between CKD and cognitive impairment, leading to a fundamental change in our understanding of these interconnected conditions[3]. This review seeks to provide a comprehensive overview of the historical context surrounding CI in CKD, tracing its evolution from an under evaluated aspect of kidney disease to a clinically significant complication[4] Through the analysis of the historical genesis of CI and its disclosure as a crucial area of research, we aim to emphasise the importance of addressing cognitive dysfunction in the management of CKD.

In addition, this literature review aims to clarify the clinical definitions and diagnostic criteria for CI in the context of CKD. Through explanation of the various definitions and criteria used to assess CI in CKD patients, we aim to provide clinicians and researchers of this area with a comprehensive framework for CI in CKD and this often-neglected complications. As CI encompasses a wide spectrum of cognitive deficits, ranging from subtle changes in memory and attention to profound impairment in executive function, a clear understanding of its clinical presentation is essential for correct diagnosis and management[5]. Furthermore, this review seeks to lay the groundwork for future research aimed at unravelling the complex interplay between kidney dysfunction and cognitive decline in CKD.

Historical perspective of kidney-brain axis

The historical perspective on the relation between CKD and cognitive dysfunction reveals a complex interaction between renal function and cognitive health. This two-way relationship, referred to as the kidney-brain axis, underscores the significant impact CKD can have on cognitive function[6]. From a common observation among CKD patients, CI can manifest in various forms, ranging from mild deficits to clinically relevant dementia. Perceiving CI in an early stage and implementing appropriate management strategies are crucial to mitigating its destructive effects on patients' quality of life. In some cases, are frequently associated with the progression of diseases and premature mortality[7].

In the framework of cognitive impairment, different definitions and stages would contribute to the progression of cognitive decline in CKD populations. According to clinical criteria CI is defined based on measurable deficits in cognitive domains without impairments in daily functioning. Mild Cognitive Impairment-Global Performance (MCI-GP) serves as an intermediary stage between normal cognitive aging and dementia[8]. These definitions provide a background for understanding the continuum of cognitive decline and the varied presentations of CI among CKD patients[9].

The apparency of MCI in CKD community has highlighted the need to recognize this condition as a distinct clinical entity, MCI-CKD. MCI, otherwise called as a "time bomb" in CKD requires an immediate attention (a multifaceted approach including early detection, comprehensive assessment, and targeted interventions to prevent further cognitive decline), due to its widespread impact on cognitive function and overall well-being[10].

A recent initiative known as European CONNECT (Cognitive Decline in Nephro - Neurology European Cooperative Target Action) Project represents a collaborative effort to address the clinical implications of CI in CKD. The CONNECT

project, funded by the COST action program, consist in a multidisciplinary network of scientists to explore the genesis and the nature of MCI in CKD patients, from a clinical and a scientific perspective. This initiative, through a coordinated research efforts among researchers, clinicians and stakeholders, seeks to address methodological challenges and facilitate the development of effective treatments for CI in CKD. The CONNECT project aims to improve outcomes for CKD patients affected by cognitive impairment[11].

Overall, understanding the historical perspective of the kidney-brain axes is essential for advancing research and clinical practice in this field. Through collaborative initiatives like CONNECT, healthcare professionals can contribute to the recognition of the MCI-CKD as a distinct clinical entity and addressing its clinical implications. In addition, these types of initiatives enhance the quality of life for CKD patients affected by cognitive dysfunction.

Kidney- Brain Structural and Hemodynamic Similarities: Microvascular Dysfunction

The intricate structural and hemodynamic similarities between the renal vasculature and brain highlight their susceptibility to systemic insults and underscore their potential role in the pathophysiology of cognitive impairment in chronic kidney disease (CKD)[12]. The strain vessel hypothesis, which is gaining ground in recent studies, posits that the microvasculature of both organs is particularly sensitive to changes in blood pressure and volume. Disruption of the blood-brain barrier and the glomerular filtration barrier can lead to albumin leakage, which points to microvascular dysfunction[13]. This pathophysiology may contribute to the observed correlation between renal dysfunction and cognitive impairment in CKD patients, taking systemic vascular health into account to understand cognitive decline.

The macula densa (MD), within the nephron, appears as the central command of the nephron with remarkable neuron-like properties. MD cells play a key role in renal sensory signaling, sensing changes in the local and systemic environment and relaying this information to the central nervous system (CNS)[14]. Key mediators of kidney-brain interaction include MD-derived systemic hormones, such as CCN1 have been implicated in modulating vascular function. Dysregulation of these signaling pathways in CKD indicates their potential involvement in the pathogenesis of cognitive impairment, providing a mechanistic link between renal dysfunction and CNS alterations[15].

The researching of kidney-brain structural and hemodynamic similarities highlights the complex interplay between renal and cognitive function. Knowing

and understanding the common pathophysiological mechanisms underlying microvascular dysfunction in both organs (kidney-brain) can help researchers and clinicals gain insight into the mechanisms that drive cognitive impairment in CKD. Moreover, the recognition of MD as a nephron central command underscores the intricate signaling pathways involved in kidney-brain interaction, offering potential targets for therapeutic intervention. (ibid)

Collaboration among nephrologists, neurologists, and researchers in related fields is essential to study further the complexity of this relationship and develop effective interventions for CKD-related cognitive impairment. Unraveling the molecular and cellular mechanisms underlying the kidney-brain interface helps researchers identify new therapeutic targets aimed at mitigating cognitive decline in this vulnerable population. These findings, in addition to contributing to knowledge about the kidney-brain connection, emphasize the importance of considering systemic factors in the assessment and management of cognitive impairment in patients with CKD.

Methodological challenges in the field of cognitive function among CKD patients

Methodological challenges in studying cognitive function among patients with chronic kidney disease (CKD) present significant obstacles to advancing our understanding of this complex relationship. Preclinical studies with animal models provide an insight into the pathophysiology of cognitive impairment (CI) in CKD. However, these studies are often limited by small sample sizes and lack of randomization, which hinders the transposition of findings into clinical practice[16]. The predominance of observational field studies requires longitudinal investigations to better define the trajectory of cognitive decline in CKD populations, addressing evidence gaps regarding the natural history of CI in this context[17].

Diverseness of CKD presents challenges in presenting results in research studies to explain the impact of different etiologies, disease stages, and treatment modalities on cognitive function[18]. Advanced and methodological assessments of glomerular filtration rate and comprehensive assessment of comorbidities are very important to increase the validity and generalizability of research findings[19]. However, its determined that albuminuria, estimated GFR and vintage of dialysis are important risk factors for MCI-CKD. *A*ddressing the aforementioned challenges helps researchers better understand the variations of cognitive impairment in CKD and tailor interventions to meet the diverse needs of affected individuals.

Accurate assessment of cognitive function in CKD patients is further complicated by age-related changes and the presence of comorbidities, which can confound test results and lead to underdiagnosis of cognitive impairment[20]. The lack of routine screening for cognitive dysfunction in CKD populations exacerbates this issue, potentially leading to missed opportunities for early identification and intervention[21]. Standardized cognitive assessments, such as the Montreal Cognitive Assessment, offer a valuable tool for identifying cognitive deficits in CKD patients[22], which is validated so far only in hemodialysis. However, these assessments must be carefully interpreted in the context of CKD, considering factors such as disease severity and treatment modalities[23,24].

Addressing methodological challenges and biases in the field of cognitive function among CKD patients is essential to advance research and improve clinical care in this area. By overcoming these obstacles, researchers can enhance our understanding of the mechanisms underlying cognitive impairment in CKD and develop more effective strategies for early detection and intervention. Collaborative efforts between researchers, clinicians, and stakeholders are crucial to address these challenges and improve outcomes for CKD patients affected by cognitive dysfunction. Through interdisciplinary collaboration and methodological rigor, the field can move closer to unraveling the complexities of cognitive impairment in CKD and improving the lives of affected individuals[25].

Perspectives for new studies

Some ambiguity continues to persist in the field of cognitive impairment associated with chronic kidney disease (CKD), highlighting the need for further research into the diagnosis, natural progression, and management of mild cognitive impairment in CKD (MCI-CKD). An important question arises regarding the definition of the difference between MCI-GP (Mild Cognitive Impairment-Global Performance) and MCI-CKD. While MCI-GP serves as an intermediate stage between normal cognitive aging and dementia in the general population[26], it remains unclear whether MCI-CKD represents an exceptional phenotype or simply an accelerated manifestation of MCI-GP within the context of CKD. Clarifying this distinction is essential for adapting diagnostic and therapeutic approaches to the specific needs of CKD patients.

Evidencing the contribution of conventional cardiovascular risk factors to the development and progression of MCI-CKD represents another critical aspect of research[27]. While CKD is associated with an increased risk of cardiovascular disease[28], the extent to which traditional risk factors such as hypertension, diabetes mellitus, and dyslipidemia influence cognitive decline in CKD patients remains

unclear[29]. Advanced research on the interplay between CKD-related factors and traditional cardiovascular risk factors may provide valuable insights and findings into the pathophysiological mechanisms underlying MCI-CKD and targeted interventions to mitigate cognitive decline in this population[30].

Establishing stable diagnostic criteria for MCI-CKD presents another challenge for joint research efforts. Currently, diagnostic criteria for MCI in CKD are based primarily on clinical assessments of cognitive function, which may lack specificity and ability to capture cognitive deficits in this population[31]. The development of standardized and validated diagnostic criteria tailored to the unique characteristics of CKD patients is essential for accurate and timely identification of MCI-CKD, addressing the implementation of early intervention and management strategies.

In addition, addressing the therapeutic potential and socio-economic burden of MCI-CKD requires interdisciplinary collaboration and comprehensive research. While various interventions, mainly pharmacological and non-pharmacological approaches, have been explored for treating cognitive impairment in CKD, their efficacy and safety remain uncertain. Moreover, the socio-economic impact of MCI-CKD, including its effects on healthcare utilization, quality of life, and caregiver burden, merits further researching to contribute in designing healthcare policy and resource allocation.

Addressing issues that require explanations on the diagnosis, natural history, and management of MCI-CKD represents an urgent need in the field of nephrology and cognitive neuroscience. Examination of the distinct characteristics of MCI-CKD, comprehensibility of its underlying pathophysiological mechanisms and therapeutic strategies, would help researchers in advancing the understanding of this complex condition and improve outcomes for CKD patients affected by cognitive impairment. Interdisciplinary collaboration and joint research efforts are essential to address these critical questions and pave the way for advancements in the diagnosis, treatment, and prevention of MCI-CKD.

Conclusions

CI stands as a significant burden among CKD patients. Despite advances in research, numerous gaps persist in comprehending the underlying pathophysiology and clinical management of Mild Cognitive Impairment in CKD (MCI-CKD). Addressing the complexities on cognitive dysfunction in CKD and developing effective interventions to alleviate its impact on patient well-being, requires an urgent attention from the scientific community.

Moving forward, future studies are essential in improving our understanding of MCI-CKD. Longitudinal follow-up is essential to elucidate the natural history of

MCI-CKD and to identify prognostic factors associated with disease progression. These studies should include diverse patient populations to capture the heterogeneity of CKD and its cognitive manifestations. Furthermore, comprehensive cognitive assessments, including both traditional neuropsychological tests and novel biomarkers, are imperative to provide a holistic assessment of cognitive function in CKD patients**.**

Additionally, jointed efforts are needed to bridge the gap between research findings and clinical practice in the management of MCI-CKD. This means developing evidence-based guidelines and best practices for the early detection, diagnosis, and treatment of cognitive impairment in CKD patients. Multidisciplinary collaboration among nephrologists, neurologists, psychologists, and other healthcare professionals is essential to enhance patient care and improve outcomes in this developing field. By addressing these challenges and advancing our understanding of MCI-CKD, we can strive towards improving the quality of life and prognosis for CKD patients affected by cognitive dysfunction.

References

1. Zoccali C, Vanholder R, Massy ZA et al. European Renal and Cardiovascular Medicine (EURECA-m) Working Group of the European Renal Association – European Dialysis Transplantation Association (ERA-EDTA). The systemic nature of CKD. Nat Rev Nephrol 2017; 13: 344–358
2. Madero M, Gul A, Sarnak MJ. Cognitive function in chronic kidney disease. Semin Dial 2008; 21: 29–37
3. 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: 353–263
4. Tyas SL, Salazar JC, Snowdon DA et al. Transitions to mild cognitive impairments, dementia, and death: findings from the nun study. Am J Epidemiol 2007; 165: 1231–1238
5. Vanderlinden JA, Ross-White A, Holden R et al. Quantifying cognitive dysfunction across the spectrum of end stage kidney disease - a systematic review and meta-analysis. Nephrology 2018; 24: 5–16
6. Sánchez-Román S, Ostrosky-Solís F, Morales-Buenrostro LE et al. Neurocognitive profile of an adult sample with chronic kidney disease. J Int Neuropsychol Soc 2011; 17: 80–90
7. Kurella Tamura M, Yaffe K. Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies. Kidney Int 2011; 79: 14–22
8. Tyas SL, Salazar JC, Snowdon DA et al. Transitions to mild cognitive impairments, dementia, and death: findings from the nun study. Am J Epidemiol 2007; 165: 1231–1238
9. DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. Lancet Neurol 2003; 2: 15–21
10. Davide Viggiano, Carsten A Waner et al Mild cognitive impairment and kidney disease: clinical aspects. NDT 2020; 1: 10-17

11. Capasso G, Waner C; CONNECT Action (Cognitive decline in Nephro-Neuurology European Cooperative Target). Present and future of CONNECT: a new and compelling project of modern medicine. NDT 2021: 37 Suppl;ii1-ii3.doi:10.1093/ndt/gfab301. PMID:34788465;PMCID:PMC8713151
12. Mogi M, Horiuchi M . Clinical interaction between brain and kidney in small vessel disease. Cardiol Res Pract 2011; 2011: 306189.
13. Ito S, Nagasawa T, Abe M, Mori T . Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. Hypertens Res 2009; 32: 115–121.
14. Gyarmati et al, BioRxiv.2021, https:// doi.org/10.1101/2021.12.06.471478
15. Christopher E Anderson et al The association of angiogenic factors and chronic kidney disease. BMC Nephrol.2018; 19(1):117.doi:10.1186/s 12882-018-0909-2
16. Viggiano D, Wagner CA, Martino G, Nedergaard M, Zoccali C, Unwin R, et al.. Mechanisms of cognitive dysfunction in CKD. Nat Rev Nephrol. (2020) 16:452–69. doi: 10.1038/s41581-020-0266-9
17. Berger I, Wu S, Masson P, Kelly PJ, Duthie FA, Whiteley W, et al.. Cognition in chronic kidney disease: a systematic review and meta-analysis. BMC Med. (2016) 14:1–10. doi: 10.1186/s12916-016-0745-9
18. Etgen T, Chonchol M, Förstl H, Sander D. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. Am J Nephrol. (2012) 35:474–82. doi: 10.1159/000338135, PMID
19. Lees JS, Welsh CE, Celis-Morales CA, Mackay D, Lewsey J, Gray SR, et al.. Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. Nat Med. (2019) 25:1753–60. doi: 10.1038/s41591-019-0627-8, PMID:
20. Murray AM. Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. Adv Chronic Kidney Dis. (2008) 15:123–32. doi: 10.1053/j.ackd.2008.01.010, PMID:
21. Roebuck-Spencer TM, Glen T, Puente AE, Denney RL, Ruff RM, Hostetter G, et al.. Cognitive screening tests versus comprehensive neuropsychological test batteries: a national academy of neuropsychology education paper. Arch Clin Neuropsychol. (2017) 32:491–8. doi: 10.1093/arclin/acx021
22. Paraizo Mde A, Almeida AL, Pires LA, Abrita RS, Crivellari MH, Pereira Bdos S, et al. Montreal Cognitive Assessment (MoCA) screening mild cognitive impairment in patients with chronic kidney disease (CKD) pre-dialysis. J Bras Nefrol 2016;38:31-41.
23. Iyasere O, Okai D, Brown E. Cognitive function and advanced kidney disease: longitudinal trends and impact on decision-making. Clin Kidney J 2017;10:89-94.
24. Cadri, Vilma. "The 6th Albanian Congress of Trauma and Emergency Surgery." *Albanian Journal of Trauma and Emergency Surgery* 6.2.6 (2022): 1-132.
25. Voskamp PWM, van Diepen M, Evans M et al. ; EQUAL Study Investigators. The impact of symptoms on health-related quality of life in elderly pre-dialysis patients: effect and importance in the EQUAL study. Nephrol Dial Transplant 2019; 34: 1707–1715
26. Lin, J. S., O'Connor, E., Rossom, R. C., et al. (2023). Screening for cognitive impairment in older adults: An Evidence Update for the US Preventive Service Task Force. Rockville, MD: Agency for Healthcare Research and Quality

27. Seliger, S. L., Siscovick, D. S., Stehman-Breen, C. O., Gillen, D. L., Fitzpatrick, A., & Bleyer, A. (2004). Moderate renal impairment and risk of dementia among older adults: the cardiovascular health cognition study. Journal of the American Society of Nephrology, 15(7), 1904-1911.
28. Rista, Elvana, et al. "p1284 Diastolic dysfunction is a strong predictor of mortality in dialysis patients." *Nephrology Dialysis Transplantation*35.Supplement_3 (2020): gfaa142-P1284.
29. Umemura T, Kawamura T, Umegaki H, Kawano N, Mashita S, Sakakibara T, Association of chronic kidney disease and cerebral small vessel disease with cognitive impairment in elderly patients with type 2 diabetes. Dement Geriatr Cogn Dis Extra. 2013 Jan;3(1):212–22.
30. Ariton DM, Jiménez-Balado J, Maisterra O, Pujadas F, Soler MJ, Delgado P. Diabetes, albuminuria and the kidney-brain axis. J Clin Med. 2021 May 27;10(11):2364. https://doi.org/10.3390/jcm10112364.
31. DeCarli C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. Lancet Neurol 2003; 2: 15–21