

Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Chronic Kidney Disease Related to Cognitive Disorders in the Elderly: A Narrative Literature Review

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ARTICLE INFO

Keywords:

Chronic kidney disease
Cognitive impairment
Erythropoietin
Elderly

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All authors have reviewed and approved the final version of the manuscript.

<https://doi.org/10.37275/bsm.v6i14.663>

ABSTRACT

Chronic kidney disease (CKD) is characterized by progressive and irreversible kidney damage, leading to the inability of the kidneys to perform their functions. Chronic kidney disease causes hypertension, anemia, vascular dysfunction, uremia, proteinuria, systemic inflammation, and oxidative stress associated with cognitive impairment. Age is a population group aged 60 years or more at risk of experiencing health problems and the consequences associated with CKD. One of the common comorbidities experienced by elderly patients with CKD is cognitive impairment. Current treatment options for CKD with cognitive impairment aimed at common risk factors, including angiotensin converting enzyme inhibitors (ACEI) and, angiotensin receptor blockers (ARBs), SGLT-2 inhibitors, GLP-1 RA, and DPP-4 inhibitors. Other interventions, such as erythropoietin (EPO) compensation and reduction of inflammation and oxidative stress, can help improve patients' clinical symptoms. This literature review aims to describe the relationship between chronic kidney disease and cognitive disorders that occur in the elderly.

1. Introduction

Chronic kidney disease (CKD) is characterized by progressive and irreversible kidney damage, leading to the inability of the kidneys to perform their functions. The prevalence of CKD has increased rapidly as a result of the higher prevalence of hypertension, diabetes mellitus, and obesity. The prevalence of CKD increases with age, with an estimated 47% of individuals aged 70 years and over in the United States developing the disease.¹

Chronic kidney disease causes hypertension, anemia, vascular dysfunction, uremia, proteinuria, systemic inflammation, and oxidative stress associated with cognitive impairment. Elderly patients

are population groups aged 60 years or more. Elderly patients are at risk for other health problems and consequences associated with CKD. One of the comorbidities that are often experienced by elderly patients with CKD is cognitive impairment.² Cognitive impairment is a condition when a person has difficulty remembering, learning new things, concentrating, or making decisions, which is quite common in CKD patients. The exact etiology of cognitive impairment in patients with CKD is not fully understood but may be a combination of factors related to the CKD process itself and microvascular changes.^{3,4} In addition to cerebrovascular causes, other potential mechanisms,

such as endothelial toxicity from the uremic state, may also be involved in cognitive impairment in CKD patients.⁵ Literature review aims to describe the relationship between chronic kidney disease and cognitive disorders that occur in the elderly.

Cognitive impairment in chronic kidney disease

Cognitive impairment is a condition when a person has difficulty remembering, learning new things or events, concentrating, or making decisions. Cognitive impairment is one of the main factors in increasing morbidity in CKD patients, but the mechanism is not widely known. Chronic kidney disease causes hypertension, anemia, vascular dysfunction, uremia, proteinuria, systemic inflammation, and oxidative stress, which are associated with the incidence of cognitive impairment.³⁻⁵

Purine metabolism is thought to cause cognitive impairment in CKD patients. Purine degradation leads to the production of hypoxanthine, which is catalyzed to xanthine and subsequently to uric acid. Impaired purine metabolism and impaired renal excretion contribute to elevated serum uric acid levels. The prevalence of hyperuricemia is increasing and is associated with risk factors for CKD. The purine metabolite hypoxanthine has been reported to cause a significant decrease in AChE activity in various brain regions, where it can lead to cognitive impairment.^{6,7}

Epidemiology of cognitive impairment in CKD

The prevalence of cognitive impairment in CKD patients ranges from 17% to 87%, depending on the severity.¹ Chronic kidney disease patients with cognitive impairment have an increased risk of death, poor quality of life, difficulty adhering to treatment, and poorer emotional quality. Among hemodialysis patients, it is also associated with an approximately twofold increased risk of death. A low estimated glomerulus filtration rate (eGFR) and albuminuria are independent risk factors for cognitive impairment. The prevalence of cognitive impairment was highest in patients with renal failure requiring dialysis. Previous

research stated that 13% of CKD patients had a normal cognitive function, while 50% had mild to moderate impairment and 37% had severe impairment.³

Risk factors

Risk factors for cognitive impairment in CKD include cerebrovascular disorders, African American and Hispanic race, dyslipidemia, diabetes mellitus, female gender, educational status, and elderly.⁸ Levels of undiagnosed depression and polypharmacy-related side effects or interactions also contribute to this disorder. Patients with kidney disease often experience significant fatigue and daytime sleepiness associated with poor sleep quality, which can contribute to further cognitive decline. Patients undergoing hemodialysis have many additional risk factors that predispose them to cognitive impairment. Dialysis procedures increase the patient's susceptibility to cognitive impairment. Hemodialysis causes volume and electrolyte fluctuations, cerebral edema, hypoperfusion, and excessive cytokine release. The frequency of hypotensive episodes during dialysis has been associated with cerebral atrophy and lacunae, while microemboli may contribute to the burden of large and small vessel cerebrovascular disease. Identification of risk factors and understanding of the impact and interaction of nonmodifiable (e.g., gender, genetics, age) and modifiable (e.g., education level, habits) risk factors for dementia has been identified as one of the research priorities to reduce the global burden of cognitive impairment.⁹⁻¹²

Pathophysiology of cognitive impairment in CKD

The causes of cognitive impairment in patients with CKD are multifactorial (Figure 1). Most CKD patients are elderly, which increases the risk of developing Alzheimer's disease. Patients with CKD have significantly disproportionate rates of cerebrovascular disease, which is an important factor in the development of CKD-associated cognitive impairment.¹²

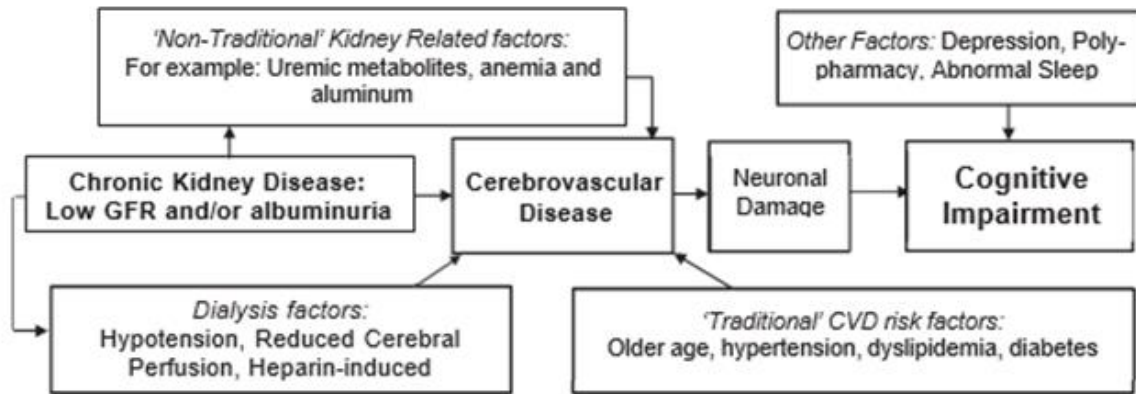


Figure 1. Pathophysiology of cognitive impairment in CKD patients.

The vascular hypothesis is the main theory of the pathogenesis of cognitive dysfunction in the general population and is based on changes in vascular anatomy accompanied by decreased cerebral blood flow resulting in impaired neural activity. Dysfunction of vascular pericytes in the brain is involved in decreased blood flow. CKD is always accompanied by an increase in blood pressure. Patients with CKD show increased blood flow to the brain (measured using the spin-labeling artery MRI modality). This increase was more pronounced in renal failure patients who were not on dialysis than in patients undergoing hemodialysis or peritoneal dialysis. End-stage renal disease (ESRD) patients undergoing hemodialysis have more complex, acute, and varied hemodynamic changes than patients undergoing peritoneal dialysis.¹³⁻¹⁵

The cognitive impairment that occurs in elderly

CKD patients is partly due to the CKD disease process itself, which creates a toxic vascular and metabolic environment consisting of chronic inflammation, oxidative stress, uremia, and systemic vascular endothelial dysfunction. Homocysteine is a very strong risk factor for stroke in CKD patients through direct neurotoxic effects, initiation of systemic inflammation, and endothelial dysfunction. The increase in homocysteine is caused by a decrease in renal clearance. Patients with CKD experience increased levels of oxidative stress caused by uremia, the production of reactive oxygen species via physiological pathways, and the inability to produce adequate antioxidant enzymes. All of these changes contribute to a vascular environment comprising systemic inflammation, high levels of oxidative stress, and endothelial dysfunction in CKD patients and create a vascular pathway to cognitive decline (Figure 2).¹⁶

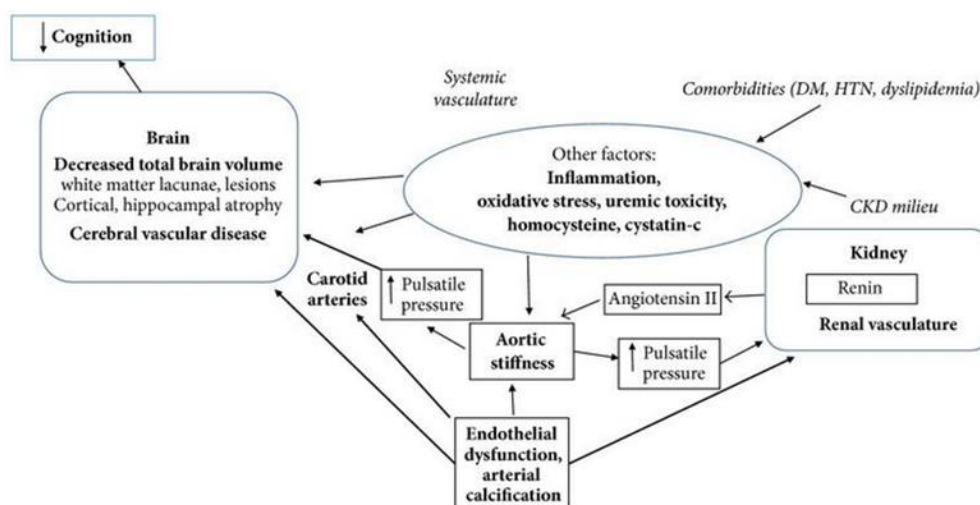


Figure 2. Systemic and cerebral vessels and cognitive function in CKD.¹⁶

The development of CKD is accompanied by the accumulation of various metabolites that are excreted by tubular filtration and secretion. Although overt uremia is usually recognized only when the GFR has decreased to less than 15 mL/min./1.73m², it is clear that the accumulation of metabolites occurs at an early stage. Uremia-associated encephalopathy is a late complication and is currently rare due to better detection of renal disease and routine use of renal replacement therapy. Treatment of renal failure with dialysis has eliminated many of the severe cognitive impairments (encephalopathy) associated with uremia. The metabolite 4-hydroxyphenylacetate is thought to contribute to CKD-associated cognitive impairment.¹⁷

Uremia is a clinical syndrome that accompanies renal failure, which is mainly associated with the retention of metabolic waste products in plasma. Neurological symptoms, including cognitive impairment, are among the earliest described clinical features of uremia. Cognitive impairment accompanying uremia has been reported to improve with dialysis or kidney transplantation. Contemporary studies show that cognitive impairment is common among patients receiving dialysis.¹⁷

It is possible that depression, including clinical and subclinical depression, contributes to impaired cognitive function. Depression, for functional and psychological reasons, can also limit the ability to properly test for cognitive impairment. Studies in

hemodialysis patients note that depression is associated with poor cognitive function, although the direction of the relationship and the exact pathophysiology have not been determined.¹⁸

The use of various drugs in the treatment of CKD (polypharmacy) also contributes to cognitive impairment. Although data on patients with CKD are limited, the high absolute number of drugs, combined with the potential for drug-drug interactions and impaired renal clearance, creates a high risk for sedation, delirium, and cognitive impairment. In addition, it is hypothesized that there is a role for sleep (or lack of sleep quality) in cognitive impairment. Dialysis patients often experience sleep disturbances, and this can lead to impaired cognitive function during the day.¹¹

Other hypotheses regarding cognitive impairment in CKD involve oxidative stress and inflammation. Elevated serum levels of free radicals and proinflammatory cytokines (interleukin-6 (IL-6), tumor necrosis factor (TNF), and IL-1beta) contribute to the development of CKD and neuroinflammation. In addition, serum levels of neuropeptide Y (NPY), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF 23) are generally elevated in CKD and promote endothelial dysfunction in the brain microcirculation. In contrast, decreased serum concentrations of alpha-klotho, the receptor for FGF-23, are also found in CKD and are associated with dementia risk (Figure 3).¹⁶

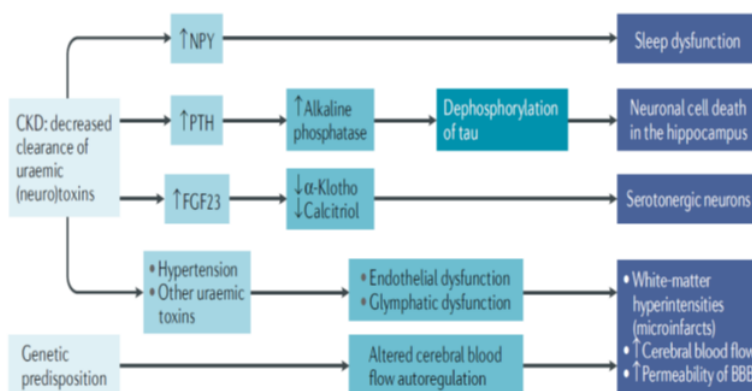


Figure 3. Mechanism of action of several uremic neurotoxins and their interactions with predisposing genetic factors.

Old age is the most significant risk factor for cognitive impairment in patients with kidney disease. Therefore, elderly patients, especially those starting dialysis, should be carefully evaluated. It is also recommended that individuals with the existing cerebrovascular disease be considered for screening. Currently, there are no guidelines stating the optimal screening test to identify cognitive impairment or dementia in elderly patients with CKD. The Montreal cognitive assessment can be thought of as a simple cognitive examination that is widely used.¹⁹ Although the Montreal cognitive assessment has not been officially validated as a screening test in patients with CKD, a small study of hemodialysis patients found that Montreal cognitive assessment scores correlated well with neurocognitive function. If the patient is found to have mild or moderate cognitive impairment on screening tests, more detailed neurocognitive testing should be considered. Further evaluation may include referral to a geriatric medicine specialist or neurologist. Neuroimaging, using either computed tomography or MRI, should be performed in any case with focal deficits, rapid decline, or recent trauma and should also be considered in patients with cognitive impairment of unknown cause. Cognitive impairment was assessed in specific cognitive domains, such as attention, memory, visuospatial ability, language skills, and executive function.¹⁹

Management of cognitive impairment in CKD

To date, most efforts to prevent or delay cognitive impairment in CKD have been very limited. Neuropsychological approaches, such as cognitive rehabilitation and art therapy, cannot slow the progression of cognitive impairment. This is because this approach does not eliminate the organic causes of this disorder. At the heart of any strategy aimed at reducing CKD-related cognitive impairment lies prevention. Thus, the focus should be on the pathophysiological mechanisms underlying the development and progression of cognitive impairment. Traditional CVD risk factor control, including the management of dyslipidemia, hypertension, and

hyperglycemia, has beneficial effects on cognitive function.^{12,20}

CKD patients have cerebral hemodynamic changes, which are likely to be the main cause of cognitive impairment. In addition to cerebrovascular causes, other potential mechanisms, such as endothelial toxicity from the uremic state, may also be involved in cognitive impairment in CKD patients. In addition, the mechanisms associated with purine nucleotides, oxidative stress, and FGF23 are still in the early stages and need further research in the future. Current treatment options for CKD with cognitive impairment are aimed at common risk factors, including ACEIs and ARBs, SGLT-2 inhibitors, GLP-1 RA, and DPP-4 inhibitors. Other interventions, such as erythropoietin compensation (EPO) and reduction of inflammation and oxidative stress, can help improve patients' clinical symptoms.^{21,22}

Anti-anemic drugs

The use of recombinant human EPO (rHuEPO), which has been established as the standard therapy for CKD-associated anemia, has shown neuroprotective effects. In a study evaluating the impact of rHuEPO on kidney damage and anemia in mice with CKD, treatment with rHuEPO not only improved anemia but also significantly decreased the expression of BACE1, presenilin-1, A β , and lipid peroxidation. In addition, rHuEPO use was associated with improved neuropsychological test scores and sensorimotor and cognitive function. Therefore, rHuEPO can be considered an effective neuroprotective agent in the context of CKD-associated cognitive dysfunction.²²

Renin-angiotensin system inhibitors

Renin-angiotensin system (RAS) plays an important role in the pathogenesis of CKD. Uremic toxins can induce the production of RAS metabolites in the central nervous system (CNS). As a result, excess angiotensin-II in the brain can cause oxidative stress leading to cognitive dysfunction. Several studies have suggested that treatment with ARBs is associated

with a lower risk of cognitive decline in dementia or Alzheimer's disease. Treatment with the angiotensin II receptor blocker telmisartan was shown to prevent spatial memory impairment by reducing brain oxidative DNA damage and lipid peroxidation and reducing cognitive impairment in a mouse model of CKD, strengthening the hypothesis that brain RAS is activated in CKD and might contribute to cognitive decline. Application of ACEI in a nephrectomy mouse model suppresses tyrosine nitrate production, oxidative stress, and ROS-NO interactions in the cerebral cortex. In general, classical treatment strategies aimed at controlling vascular risk factors, such as ACEs or ARBs, can improve cognitive function.^{23,24}

Anti-inflammatory agents

Inflammation is known to be associated with the development of CKD. Recent studies have found that peripheral inflammation can significantly contribute to central inflammation in different disease settings. Intestinal microbiota-mediated peripheral inflammation can induce central inflammation in transgenic mice. Therefore, the inhibition of CKD-associated peripheral inflammation to prevent cognitive impairment is attracting much attention. For example, elevated uric acid may modulate the NLR pyrin domain-containing protein 3 (NLRP3)/IL-1 β -related pathway by ROS activation and consequently cause vascular endothelial cell damage, which is closely associated with micro-inflammation, oxidative stress, and impaired lipid metabolism in the early stages of CKD.²⁵

Anti-diabetic drugs

Type 2 diabetes mellitus (DMT2) is a major cause of CKD. The use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1RA) receptor agonists have been shown to correlate with a reduced risk of cardiovascular and renal events. Previous studies have shown that SGLT-2 inhibitors have strong neuroprotective properties. In clinical trials of patients with T2DM, this agent has been

shown to reduce albuminuria and proteinuria by 30-50%. Meanwhile, an SGLT2 inhibitor was detected in the central nervous system, and empagliflozin has been shown to reduce the amyloid load in the cortical regions of APP/PS1xd/db rats. Empagliflozin has a beneficial effect on cognitive function, which may be related to an increase in neurotrophic factors in the brain. Other SGLT2 inhibitors, such as canagliflozin and dapagliflozin, have been shown to have AChE inhibitory activity.²⁶

Dipeptidyl peptidase-4 (DPP-4) inhibitors are well tolerated in T2DM patients with CKD and may reduce major risk factors for diabetic nephropathies, such as hyperglycemia and albuminuria. Preclinical and clinical studies have shown that DPP-4 inhibitors can exert a significant pleiotropic effect in CKD. Linagliptin, a DPP-4 inhibitor, has shown beneficial effects in protecting against the occurrence or progression of cognitive decline and/or reducing the risk of cognitive impairment or dementia.²⁷

Anti-vascular calcification

Vascular calcification can induce renal dysfunction through high phosphate levels in a CKD mouse model with nephrectomy. HMGB-1, a DNA-binding protein involved in inflammation, was recently identified as a proinflammatory mediator of tissue injury. A cross-sectional study revealed that HMGB-1 was significantly increased in CKD patients and correlated with glomerular filtration rate. Another study demonstrated that HMGB1 is involved in CKD-associated vascular calcification through a mechanism involving catenin.²⁸

Other treatments

Klotho, as an anti-aging protein primarily expressed in the kidney, is significantly associated with the development of CKD. Klotho deficiency causes white matter hyperintensity, micro bleeding, microinfarction, and cerebral atrophy through chronic inflammation, endothelial dysfunction, and vascular calcification. Therefore, changes in klotho levels may play a role in the development of cognitive impairment

in CKD patients. Recombinant klotho protein may be a hope of treatment or prevention for CKD with cognitive impairment in the near future.²⁹

2. Conclusion

Patients with CKD are at a higher risk for developing cognitive impairment, with elderly patients being at the highest risk. Control of CVD risk factors, as recommended by current standards of care, is an action that can be taken to limit the development of cognitive impairment.

3. References

1. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, et al. Global prevalence of chronic kidney disease—a systematic review and meta-analysis. *PLoS One*. 2016; 11(7): e0158765.
2. Gela YY, Getu AA, Adane A, Ayal BM, Akalu Y, et al. Cognitive impairment and associated factors among chronic kidney disease patients: a comparative cross-sectional study. *Neuropsychiatric Disease and Treatment*. 2021; 17: 1483.
3. Zammit AR, Katz MJ, Bitzer M, Lipton RB. Cognitive impairment and dementia in older adults with chronic kidney disease: a review. *Alzheimer's disease and associated disorders*. 2016; 30(4): 357.
4. Tamura MK, Yaffe K, Hsu CY, Yang J, Sozio S, et al. Cognitive impairment and progression of CKD. *American Journal of Kidney Diseases*. 2016; 68(1): 77-83.
5. Kurella M, Chertow GM, Fried LF, Cummings SR, Harris T, et al. Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *Journal of the American Society of Nephrology*. 2005; 16(7): 2127-33.
6. Mullins LJ, Conway BR, Menzies RI, Denby L, Mullins JJ. Renal disease pathophysiology and treatment: contributions from the rat. *Disease Models & Mechanisms*. 2016; 9(12): 1419-33.
7. Yamaguchi J, Tanaka T, Nangaku M. Recent advances in the understanding of chronic kidney disease. *F1000Research*. 2015; 4.
8. Kazancioğlu R. Risk factors for chronic kidney disease: an update. *Kidney International Supplements*. 2013; 3(4): 368-71.
9. Sharma M, Doley P, Das HJ. Etiological profile of chronic kidney disease: A single-center retrospective hospital-based study. *Saudi Journal of Kidney Diseases and Transplantation*. 2018; 29(2): 409.
10. Hannan M, Steffen A, Quinn L, Collins EG, Phillips SA, et al. The assessment of cognitive function in older adult patients with chronic kidney disease: an integrative review. *Journal of Nephrology*. 2019; 32(2): 211-30.
11. Pais R, Ruano L, Moreira C, Carvalho OP, Barros H. Prevalence and incidence of cognitive impairment in an elderly Portuguese population (65–85 years old). *BMC Geriatrics*. 2020; 20(1): 1-10.
12. Drew DA, Weiner DE, Sarnak MJ. Cognitive impairment in CKD: pathophysiology, management, and prevention. *American Journal of Kidney Diseases*. 2019; 74(6): 782-90.
13. Viggiano D, Wagner CA, Martino G, Nedergaard M, Zoccali C, et al. Mechanisms of cognitive dysfunction in CKD. *Nature Reviews Nephrology*. 2020; 16(8): 452-69.
14. e Silva ACS, Miranda AS, Rocha NP, Teixeira AL. Neuropsychiatric disorders in chronic kidney disease. *Frontiers in Pharmacology*. 2019: 932.
15. Bugnicourt JM, Godefroy O, Chillon JM, Choukroun G, Massy ZA. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. *Journal of the American Society of Nephrology*. 2013; 24(3): 353-63.
16. Di Rosa M, D'Alia S, Guarasci F, Soraci L, Pierpaoli E, et al. Cognitive impairment, chronic kidney disease, and 1-year mortality

- in older patients discharged from acute care hospital. *Journal of Clinical Medicine*. 2020; 9(7): 2202.
17. Tamura MK, Chertow GM, Depner TA, Nissenson AR, Schiller B, et al. Metabolic profiling of impaired cognitive function in patients receiving dialysis. *Journal of the American Society of Nephrology*. 2016; 27(12): 3780-7.
 18. Li G, Zhao M, Cheng X, Zhao T, Feng Z, et al. FG-4592 improves depressive-like behaviors through HIF-1-mediated neurogenesis and synapse plasticity in rats. *Neurotherapeutics*. 2020; 17(2): 664-75.
 19. Dautzenberg G, Lijmer J, Beekman A. Diagnostic accuracy of Montreal Cognitive Assessment (MoCA) for cognitive screening in old age psychiatry: Determining cutoff scores in clinical practice-avoiding bias caused by healthy controls. *Int J Geriatr Psychiatry*. 2020; 35(3): 261-9.
 20. Xie Z, Tong S, Chu X, Feng T, Geng M. Chronic kidney disease and cognitive impairment: The kidney-brain axis. *Kidney Diseases*. 2022; 3: 1.
 21. Choi B, Crouzet C, Lau WL, Cribbs DH, Fisher MJ. Cerebral blood flow in chronic kidney disease. *Journal of Stroke and Cerebrovascular Diseases*. 2021; 30(9): 105702.
 22. Reza-Zaldivar EE, Sandoval-Avila S, Gutierrez-Mercado YK, Vazquez-Mendez E, et al. Human recombinant erythropoietin reduces sensorimotor dysfunction and cognitive impairment in rat models of chronic kidney disease. *Neurologia*. 2020; 35(3): 147-54.
 23. Laffer CL, Eljovich F, Sahinoz M, Pitzer A, Kirabo A. New insights into the renin-angiotensin system in chronic kidney disease. *Circ Res*. 2020; 127(5): 607-9.
 24. Nakagawa T, Hasegawa Y, Uekawa K, Kim-Mitsuyama S. Chronic kidney disease accelerates cognitive impairment in a mouse model of Alzheimer's disease through angiotensin II. *Exp Gerontol*. 2017; 87(Pt A): 108-12.
 25. Piperidou A, Loutradis C, Sarafidis P. SGLT-2 inhibitors and nephroprotection: current evidence and future perspectives. *J Hum Hypertens*. 2021; 35(1): 12-25.
 26. Wicinski M, Wodkiewicz E, Gorski K, Walczak M, Malinowski B. Perspective of SGLT2 inhibition in treatment of conditions connected to neuronal loss: focus on Alzheimer's disease and ischemia-related brain injury. *Pharmaceuticals*. 2020; 13(11): 379.
 27. Coppolino G, Leporini C, Rivoli L, Ursini F, di Paola ED, et al. Exploring the effects of DPP-4 inhibitors on the kidney from the bench to clinical trials. *Pharmacol Res*. 2018; 129: 274-94.
 28. Paudel YN, Angelopoulou E, Piperi C, Othman I, Aamir K, et al. Impact of HMGB1, RAGE, and TLR4 in Alzheimer's disease (AD): from risk factors to therapeutic targeting. *Cells*. 2020; 9(2): 383.
 29. Degaspari S, Tzanno-Martins CB, Fujihara CK, Zatz R, Branco-Martins JP, Viel TA, et al. Altered KLOTTHO and NF-kappaB-TNF-alpha signaling are correlated with nephrectomy induced cognitive impairment in rats. *PLoS One*. 2015; 10(5): e0125271.