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Behavioral Sciences

Cognitive Function of Patients with Chronic Renal Insufficiency in Hemodialysis: A Systematic Review

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ABSTRACT – The objective was to systematically review the relationship between Chronic Kidney Failure and Hemodialysis with cognitive function. This systematic review followed the parameters proposed by PRISMA. The search for articles was carried out in the PubMed database. A total of 113 articles were found, of which 31 were selected for analysis. Analyzing the studies' samples, it was found that 19.3% of them had a control group, that the most used instrument was the Mini-Mental State Examination (41.9%), and that patients of older age and patients with longer hemodialysis treatment had worse cognitive scores. It is concluded that HD can reduce the cognitive function of people with CKF.

KEYWORDS: Renal Dialysis, Chronic Kidney Failure, Cognition, Systematic Review

Função Cognitiva de Pacientes com Insuficiência Renal Crônica em Hemodiálise: Uma Revisão Sistemática

RESUMO – O objetivo foi revisar sistematicamente a relação da Insuficiência Renal Crônica e da Hemodiálise com a função cognitiva. Esta pesquisa de revisão sistemática seguiu os parâmetros propostos pelo PRISMA. A busca dos artigos foi realizada na base de dados PubMed. Foram encontrados 113 artigos, sendo que destes 31 foram selecionados para análise. Analisando a amostra dos estudos verificou-se que 19,3% dos estudos tiveram grupo controle, que o instrumento mais utilizado foi Mini Exame do Estado Mental (41,9%) e que pacientes com idade mais avançada e os pacientes com mais tempo de tratamento hemodialítico tinham piores escores cognitivos. Conclui-se que a HD pode reduzir a função cognitiva de pessoas com IRC.

PALAVRAS-CHAVE: Diálise Renal, Falência Renal Crônica, Cognição, Revisão Sistemática

Chronic Kidney Failure (CKF) is becoming increasingly common, affecting 3.6 million people worldwide (Marinho et al., 2017). It is considered a public health problem due to morbidity and mortality, the high cost of treatment, the social impact it causes on the patient (Karatas et al., 2018), multisystem complications (Wuttke et al., 2019), and high hospitalization rates (Alcalde & Kirsztajn, 2018).

CKF stands out due to its high incidence and prevalence rate, which reach 194 and 610 patients per million population (PMP), respectively (Thomé et al., 2019). These numbers tend to increase considerably due to population aging and its morbidity profile, which aggravates the epidemiological picture of the pathology (Miranda et al., 2016), and because its main risk factors such as diabetes mellitus, systemic arterial hypertension, glomerulonephritis, metabolic syndrome, and urological diseases are also at high rates of increase (Li & Ma, 2017).

In the last two decades, advances in the treatment of CKF have helped increase the survival of people who have this morbidity (Msaad et al., 2019). Among the types of treatment, hemodialysis (HD) represents the main alternative. Currently, about 2 million people worldwide are on HD,

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and this number in Brazil reaches 126,583 thousand people, according to the annual survey carried out by the Brazilian Society of Nephrology (SBN) (Thomé et al., 2019).

Patients with CKF undergoing HD face significant lifestyle changes that seriously affect biopsychosocial aspects of health (Johnston, 2016; Ren et al., 2019). Several studies indicate that HD patients have worsening of their health conditions, loss of muscle mass, frailty (Kamijo et al., 2018), depression (Khan et al., 2019), poor sleep quality and health (Ren et al., 2019), malnutrition (Bousquet-Santos et al., 2019) and worsening of cognitive function (Erken et al., 2019).

Cognitive impairment is very common in CKF (Van Sandwijk et al., 2016), and HD seems to have an even higher negative impact on patients' cognitive function due to circulatory stress and cerebral hypoperfusion caused by the treatment (Wolfgram, 2018).

Cognitive function can affect dialysis treatment in several ways, impair decision-making ability and therapeutic involvement, reduce self-care capacity, and lead to low adherence to therapy and associated lifestyle restrictions (Wilson et al., 2018).

As a consequence of this cognitive impairment, there is a lower perception of quality of life and a higher risk of hospitalization and mortality in these patients (Wilson et al., 2018). Thus, periodic monitoring should be part of the monitoring of HD patients, which is essential to identify and prevent the deleterious effects caused by the disease (Bousquet-Santos et al., 2019).

In 2010, intending to verify/identify the panorama of CKF in Brazil, the SBN began to carry out the Brazilian Chronic Dialysis Survey, which aims to collect individual data from patients on dialysis throughout Brazil. However, the results are limited to prevalence and incidence data and describe the characteristics of the health institutions of patients on chronic dialysis in Brazil (Thomé et al., 2019) and do not assess the cognitive function of these people, which leaves a gap in the assessment of this specific population.

Longitudinal international studies evaluated the cognition of this population (Foster et al., 2016; Mcadams-Demarco et al., 2015) and showed a worsening in cognition as the Glomerular Filtration Rate (GFR) of patients decreases. Therefore, this study aimed to systematically review the relationship between CKF and HD with cognitive function.

METHOD

This systematic review research followed the parameters proposed by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Liberati et al., 2009), which consists of a checklist of 27 items and a flow diagram in four phases, considered essential for transparent reporting of a systematic review, given that these types of study are useful tools for understanding evidence.

The search for articles was performed in the PubMed database, using the following inclusion criteria: a) studies carried out with human beings; b) studies published from January 2015 to March 2020; c) studies with patients undergoing dialysis therapy, and; d) international studies. We opted for international studies since this topic is still little explored in Brazil. As a search strategy, the descriptors "Renal Dialysis", "Renal Insufficiency", "Chronic" and "Cognition" were used. The searches were carried out from the 15th to the 22nd of March 2020. A total of 113 articles were found, 40 of which were excluded because they did not cover the study theme, 25 because they were reviews, comments, or case reports, and 17 because they used other types of treatment. Thus, 31 articles were selected for full reading, as shown in the figure below (Figure 1).

The selected articles were evaluated by the instrument used and the main results considered the relationship between CKF and HD with cognitive function.

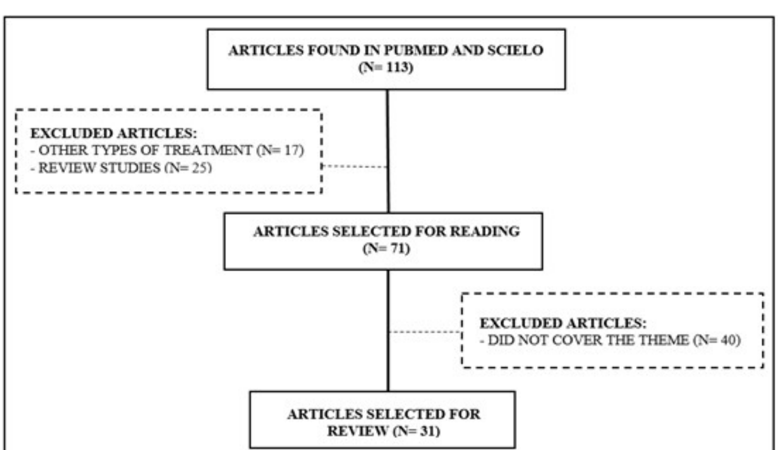

Figure 1.The search strategy used for the selection of articles in the systematic review.

RESULTS

The results of the search performed in the PubMed database are described in Table 1, in which 31 (thirty-one) articles were selected.

Analyzing the sample of studies, it was found that 19.3% (n= 6) of the studies had a control group, three of them (9.6%) with paired samples between the groups (Erken et al., 2019; Malik et al., 2017; Shaker et al., 2018). Only one study (Stringuetta et al., 2018) had a randomized sample (3.2%). The most used instrument was the Mini-Mental State Examination (41.9%; n= 13) (Abdulan et al., 2019; Adame Perez et al., 2018; Anwar et al., 2015; Chiu et al., 2019; Coppolino et al., 2018; Henry et al., 2018; Kitaguchi et al., 2015; Murray et al., 2016; Prelevic et al., 2018; Romijn et al., 2015; Shaker et al., 2018; Stringuetta et al., 2018; Tasmoc et al., 2016).

A study (Prelevic et al., 2018) analyzed in this research showed that insulin-like growth factor 1 (IGF-1) can be considered a biomarker of cognitive functioning.

In addition, the main results that the studies found were that HD patients have accelerated brain aging (Chiu et al., 2019), a higher prevalence of cardiovascular problems (Wei et al., 2019), and transient decline in cerebral blood flow (Findlay et al., 2018; Stringuetta et al., 2018), factors that influence cognitive decline. Anemia (Shaker et al., 2018) and frailty (Chao et al., 2017; Mcadams-Demarco et al., 2015), common problems in HD patients, were also found to influence cognitive loss.

Already at the beginning of treatment, executive function (Kurella Tamura et al., 2017) and cerebral ischemia (Malik et al., 2017), according to this review, are higher and thus influence the cognitive loss of this HD population.

Another negative influence of HD on cognitive function (according to the studies analyzed) is that patients of older age and patients with longer hemodialysis treatment have worse cognitive scores (Gesualdo et al., 2017).

When comparing HD with other forms of treatment, it was evidenced that HD patients have a higher cognitive impairment, both concerning pre-dialysis patients (Erken et al., 2019) and when compared with kidney transplantation (Anwar et al., 2015) and peritoneal dialysis (Neumann et al., 2018). This is due to the greater severity of the disease in HD patients, which influences this loss (Coppolino et al., 2018), taking into account the eGFR cut-off point < 30 mL/min/1.73 m^2 where the worsening of cognitive function occurs significantly accentuates (Murray et al., 2016).

Table 1
Synthesis of the studies' results selected for evaluation

Author/ Year	Objective	Sample	Assessment Instrument	Results
(Wilkinson et al., 2019)	To investigate postural stability in a group of patients with CKF who do not require RRT.	n= 30	Montreal Cognitive Assessment-Basic (MoCA)	Postural stability is associated with worse physical and cognitive functioning.
(Wei et al., 2019)	To determine the relationship between serum klotho and cerebrovascular disease in hemodialysis patients.	n= 88	Neuropsychological battery	The serum level of klotho is a potential predictor of cerebrovascular disease.
(Chiu et al., 2019)	To investigate whether general cognitive function and brain changes are compatible with an accelerated aging phenotype and whether they can inform possible underlying pathophysiological mechanisms.	EG= 56 CG= 60	(MMSE)	HD patients show an accelerated brain aging phenotype, even after taking into account the effects of age, diabetes, and depression.
(Erken et al., 2019)	Assess relatively young HD patients with fewer comorbidities and identify clues for early detection of cognitive impairment with the help of cognitive subscale scores.	EG= 103 CG= 37	(MoCA)	Cognitive impairment was more common in HD patients compared with pre-dialysis CKF patients.
(Shaker et al., 2018)	To evaluate the effect of anemia correction on cerebral blood flow concerning cognitive functions.	EG= 120 CG= 60	(MMSE)	As anemia improved, cognitive functions improved.
(Findlay et al., 2018)	To explore whether HD is associated with changes in cerebral blood flow and to determine whether these changes are related to intradialytic cognitive dysfunction.	n= 97	Neuropsychological battery	HD patients experience a transient decline in cerebral blood flow, correlating with cognitive dysfunction.
(Abdulan et al., 2019)	To describe the prevalence of malnutrition and cognitive impairment.	n= 81	(MMSE)	The study confirms the important correlation between malnutrition and cognitive impairment.

Table 1
Cont.

Author/ Year	Objective	Sample	Assessment Instrument	Results
(Otobe et al., 2019)	To evaluate the prevalence of Mild Cognitive Impairment and the relationship with physical function in elderly people with pre-dialysis CKF.	n= 120	(MoCA)	The association between MCI and reduced gait speed supports the possible interaction between physical and cognitive functions and the need for early screening.
(Adame Perez et al., 2018)	To compare differences in body composition, quality of life, mental health, and cognitive and vitamin D status with the use of health services by frail and non-frail adults with diabetes mellitus and CKF.	n = 41	(MMSE)	All participants had MMSE scores indicative of normality.
(Stringuetta et al., 2018)	To evaluate the effects of intradialytic aerobic training (IAT) on cerebral blood flow and cognitive impairment in HD.	CG= 15 EG= 15 controlled and randomized	(MMSE)	IAT improves cognitive impairment and cerebral blood flow.
(Coppolino et al., 2018)	Assess functional impairment, general and cognitive health, and the possible relationship between these types of dysfunctions and the severity of renal impairment.	n= 271	(MMSE)	The severity of renal dysfunction is correlated with that of cognitive impairment.
(Polinder-bos et al., 2018)	To evaluate the acute effect of conventional HD on cerebral blood flow (CBF).	n= 12	Neuropsychological assessment battery	No correlation was found between cognitive function and structural markers of brain injuries.
(Henry et al., 2018)	To examine the relationship between the duration of the interdialytic interval and reports of cognitive dysfunction.	n= 26	(MMSE)	Cognitive impairment appears to worsen soon after HD treatment and improves during the intradialytic interval.
(Prelevic et al,. 2018)	To analyze risk factors for the decline in cognitive function in these patients.	n= 93	(MMSE)	IGF-1 can be considered a biomarker of cognitive functioning.
(Neumann et al., 2018)	To compare, in one year, the cognitive function of peritoneal patients to HD patients.	n= 271	Trail Making Test-B and d2-Revision-Test	Peritoneal dialysis is associated with better cognitive function for one year compared with HD.
(Gesualdo et al., 2017)	To assess the cognitive capacity of patients with CKF on HD and its relationship with sociodemographic and clinical characteristics.	n= 99	Addenbrooke's Cognitive Examination	Older individuals and those with longer HD had greater cognitive impairment.
(Chao et al., 2017)	To examine the differences in cortical activities of patients with CKF, based on their levels of frailty, and to explore the clinical implications.	n= 36	Electroencephalo-graphic data	Frailty may have more subtle neurophysiological influences in addition to cognitive dysfunction.
(Neumann et al., 2017)	To assess the reliability of the literature on standard CT in the population of patients with CKF.	n= 767	Trail Making Test-B and the German d2-Revision Test	Results on cognitive functioning may be biased. Non-visual and non-verbal cognitive testing can be a valuable resource.
(Kurella Tamura et al., 2017)	To assess the trajectory of cognitive function in a contemporary cohort of adults with advanced CKF before and after dialysis initiation.	n= 212	The battery of tests as z scores.	Initiation of dialysis was associated with loss of executive function, with no change in other aspects of cognition.
(Malik et al., 2017)	To describe the oxygenation values of the brain and hands in patients with CKF and their changes during HD.	EG= 27 CG= 17	Regional oxygen saturation	Tissue ischemia worsens after initiation of HD. This observation may contribute to the understanding of the etiology of the cognitive deficit.
(Foster et al., 2016)	To assess cognitive impairment in advanced chronic kidney disease.	n= 385	(MoCA)	The rate of impairment is high and global, affecting all aspects of cognition, and is likely vascular in nature.
(Kurella Tamura et al., 2016)	Identify and validate uremic metabolites associated with cognitive impairment using two cohorts of patients on maintenance dialysis.	n= 180	Trail Making Test Part B and the Digit Symbol Substitution.	Four metabolites related to the metabolism of phenylalanine, benzoate, and glutamate can be used as markers.

Table 1
Cont.

Author/ Year	Objective	Sample	Assessment Instrument	Results
(Tasmoc et al., 2016)	To assess the relationship between arterial stiffness and cognitive impairment in a cohort of HD patients.	n= 72	(MMSE)	Cognitive impairment was associated with pulse wave velocity. More evidence is needed to support arterial stiffness as a long-term predictor of cognitive decline.
(Dixon et al., 2016)	Longitudinal follow-up of the effect on cognitive performance of changing the dialysis treatment modality from conventional hemodialysis to nocturnal hemodialysis.	n= 77	Neuropsychological tests	Cognitive performance remained stable, except for an improvement in psychomotor processing speed and a decline in verbal fluency.
(Murray et al., 2016)	To identify mechanisms that contribute to the increased risk of cognitive impairment in patients with CKF.	n= 554	(MMSE)	Cognitive function was significantly worse in participants with eGFR < 30 mL/min/1.73 m^2.
(Mcadams-Demarco et al., 2015)	To verify whether frailty may also be associated with impaired cognitive function in adults of all ages undergoing HD.	n= 324	Trail Making Testing A and B	In adult HD patients, frailty is associated with worse cognitive function.
(Anwar et al., 2015)	To compare the impact of hemodialysis and kidney transplantation on cognitive functions in patients with CKF.	n= 100	(MMSE)	Kidney transplantation is superior to HD in terms of improving cognitive performance.
(Kitaguchi et al., 2015)	Evaluate plasma Aβ levels and cognitive function longitudinally.	n= 30	(MMSE)	HD removes Aβ from the blood, may alter Aβ influx, and help maintain cognitive function.
(Chen et al., 2015)	To investigate the effect of hemodialysis (HD) on cognitive dysfunction in patients with CKF.	G1= 58 in HD G2= 26 with CFK without HD G3= 32 healthy.	The battery of neuropsychological tests	HD can cause an adverse effect on cognitive function in patients.
(Schneider et al., 2015)	Assess cognitive function using a generalized test battery and avoid exclusionary effects of circadian variations.	n= 28	The battery of neuropsychological tests	Improvements in memory functions, executive functions, and psychomotor skills after a single session.
(Romijn et al., 2015)	To investigate the relationship between renal function and cognition in patients from a memory clinic.	n= 581	(MMSE)	Association between mild CKF and impaired cognitive function.

DISCUSSION

In this systematic review, it was found that a low percentage of the studies in this review had a control group. Not having the comparison group weakens the considerations about the study since experimental studies are stronger in their evidence when comparing the experimental group and the control group (Thiese, 2014). In addition, only one study was randomized, which demonstrates the difficulty of carrying out studies with this type of sampling in renal clinics.

The Mini-Mental State Examination (MMSE) developed by Folstein et al. (1975) was the most used instrument, which was also evidenced in the systematic review and meta-analysis performed by Vanderlinden et al. (2018), who sought to identify the neurocognitive tests used in patients with CKF. The MMSE can detect significant differences when compared to healthy individuals, thus being a safe instrument for screening for dementia, indicating possible deficits in global functioning, attention, and processing speed in this population (Vanderlinden et al., 2018).

It is noteworthy that IGF-1 was found in this review as a biomarker of cognitive functioning, as reduced serum levels of IGF-1 decrease the clearance of amyloid-beta protein in the brain, potentiate inflammation (Nilsson et al., 2015), and are associated with high cardiovascular risk (Beberashvili et al., 2013). Thus, low serum IGF-1 levels are a risk factor for cognitive impairment.

According to the studies analyzed, patients with more advanced age have higher cognitive impairment. The research carried out by Viana et al. (2019) evaluated the cognition of the elderly (60 years and over) and very elderly (80 years and over) on HD and found that the prevalence of any deficit was higher among the very elderly (72% and 94%, p = 0.007).

A high rate of cognitive impairment is associated with older age (Foster et al., 2016). In young and middle-aged patients with CKF, the prevalence of cognitive impairment ranges from 10% to 30%, rising to 30% to 55% in patients older than 75 years (Kurella Tamura et al., 2010).

Cognitive function decreases considerably as the disease progresses as it has a higher deterioration when comparing the stages of the same (stages 1 to 5) (Brodski et al., 2019). Early-stage CKF provides drops in processing speed, attention, response speed, and short-term memory capacity. In a moderate stage, kidney disease causes deficits in executive functioning, verbal fluency, logical memory, orientation, and concentration. In stage 5 in HD, significant deficits are manifested in all cognitive domains, along with cognitive control, immediate and delayed memory, visuospatial impairment, and general cognitive impairment (Brodski et al., 2019).

In this sense, it is noteworthy that GFR is associated with cognitive function, as the prevalence of cognitive dysfunction increases linearly with the decline in GFR (Berger et al., 2016). The independent association between cognitive impairment and CKF progression was assessed by the MMSE during a median of 6.1 years of follow-up, and the results showed that a GFR below 30 mL/min/1.73 m^2 was associated with a 47% increase in cognitive decline, regardless of disease and risk factors (Kurella Tamura et al., 2016).

Regarding studies that evaluated cognitive impairment in the different treatments used in CKF, the main finding of this review is the high prevalence of cognitive impairment in HD patients. When comparing HD with other forms of treatment, it was shown that HD patients have greater cognitive impairment (O'Lone et al., 2016), a fact that can be explained by the higher severity of the disease in these patients.

Point prevalence data suggest that dialysis patients manifest cognitive problem rates 3 to 5 times higher than the general population, with executive function being the most commonly affected cognitive domain (Wilson et al., 2018). This type of renal replacement therapy, while beneficial in terms of eliminating uremic toxins, also contributes to cognitive decline by causing rapid fluid and osmotic changes (Van Sandwijk et al., 2016).

HD causes many problems in the human body, including brain aging (Tsuruya & Yoshida, 2018) and cardiovascular problems (Oh et al., 2018; Foster et al., 2016), which causes a transient decline in cerebral blood flow. (Jiang et al., 2016); anemia (Drew et al., 2019) and frailty (Kallenberg et al., 2016), factors that can influence cognitive decline. These and other problems arising from HD accelerate pathophysiological mechanisms that promote neurological impairment and can cause chronic degenerative changes in the kidneys and, consequently, in the brain (Chen et al., 2015), which highlights the relationship between kidney and cognitive problems.

Some studies provide evidence that it is not just CKF-specific factors responsible for the cognitive decline but include the HD process itself. One area of focus is the potential for ischemic damage and intradialytic cerebral hypoperfusion due to variations in blood flow that can occur during HD and the induction of an acute decline in cerebral blood flow (Wolfgram, 2018). In addition to these aspects, antihistamines, opioids, and aluminum use, and intradialytic hypotension contribute to the decline of cognitive function (Schneider et al., 2015).

A gap found in the evaluation of these studies is related to the lack of randomized clinical trials to show a greater relationship between cause and effect, considering that only six studies had control groups for comparison and one had a randomized sample. Another essential point that can be researched in the future is the proposition of a specific classification for renal patients on HD concerning the cognitive function evaluated by the Mini-Mental State Examination, given this instrument is specific for the elderly.

FINAL REMARKS

It is concluded in this study that there is a relationship between CKF and HD with cognitive decline, emphasizing that this type of treatment, over time, increasingly reduces cognitive function. In this sense, intervention programs focused on the cognitive rehabilitation of HD patients should be stimulated, both intradialytically and in periods contrary to treatment.

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