Frailty and Cognitive Impairment in Chronic Kidney Disease

13

Kazuhiko Tsuruya

Abstract

Recently, accumulating evidence has been published on cognitive impairment in patients with chronic kidney disease (CKD). It has been shown that brain atrophy is prominent in patients receiving hemodialysis or peritoneal dialysis, and the significant association between brain atrophy and frequency of rapid decline in blood pressure during the hemodialysis session was documented. Recently, we reported a close association between gray matter atrophy and executive dysfunction in CKD patients, suggesting the importance of preventing brain atrophy for the prevention of cognitive impairment. It has been reported that frailty, a common geriatric syndrome that embodies an elevated risk of catastrophic declines in health and function among older adults, is associated with poor cognitive function, cognitive decline, and dementia in older adults with and without CKD. A number of traditional and nontraditional vascular factors and nonvascular factors are strongly implicated in the pathophysiological relationship among CKD, cognitive decline, and frailty. Several recent randomized controlled trials of elderly individuals without dementia have demonstrated that exercise training improved cognitive function with an increase in brain volume. Experimental studies have shown that exercise decreased the amount of β-amyloid (Aβ) oligomers in addition to depositing Aβ in the brain. Alternatively, some other studies have demonstrated that physical training increases angiogenesis, synaptogenesis, and neurogenesis, especially in hippocampus and in gyrus dentatus and initiates the upregulation of numerous neurotrophic factors such as BDNF and IGF-1 in the brain, especially in hippocampus. Accordingly, physical exercise training should be implemented to prevent and treat frailty and cognitive impairment in the elderly CKD patients.

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13.1 Introduction

Recently, accumulating evidence has been published on cognitive impairment in patients with chronic kidney disease (CKD), especially in patients receiving hemodialysis (HD) and peritoneal dialysis (PD). It has become clear that the prevalence of cognitive impairment is increased in not only dialysis patients, but also in non-dialysis-dependent CKD (NDD-CKD) patients [1, 2]. The symptoms and characteristics of cognitive impairment in patients with CKD are characterized by vascular cognitive impairment, believed to be caused by damaged blood vessels in the brain, or cerebrovascular disease, rather than Alzheimer-type dementia [3, 4]. In this article, I discuss cognitive impairment in CKD patients with regard to brain atrophy, factors associated with cognitive impairment, and the association of dialysis modality with cognitive impairment in the first half of this article, and the association between frailty and cognitive impairment in the second half.

13.2 Cognitive Impairment in CKD Patients

13.2.1 Brain Atrophy in Patients Receiving HD

Dialysis patients have a higher prevalence of brain atrophy, even at younger age, than the general population. This suggests the involvement of a mechanism that cannot be explained only by aging. We previously assessed the extent of brain atrophy in 55 HD patients without clinically overt neurological signs and symptoms, with a mean age of 52 ± 11 (SD) years and a mean HD duration of 7 ± 6 (SD) years and in 35 healthy individuals, with a mean age of 42 ± 14 (SD) years. Brain atrophy was assessed by the ventricular–brain ratio (VBR), calculated as the ratio of the ventricular area to the whole brain area on the maximum MRI slice and compared between the two groups. The severity of periventricular hyperintensity (PVH) and the number of lacunae were also regarded as ischemic brain lesions. The VBRs at all age groups were significantly higher in HD than in controls. The results showed that HD patients had significantly higher number of lacunae and had more advanced PVH than did controls. Both the number of lacunae and the severity of PVH were significantly correlated to VBR in HD. According to these findings, we concluded that the rapid progression of brain atrophy was related to the asymptomatic ischemic brain lesions in our HD patients. Such data indicated that cerebral ischemia might be a causative mechanism of brain atrophy in chronic HD patients (Fig. 13.1) [5].

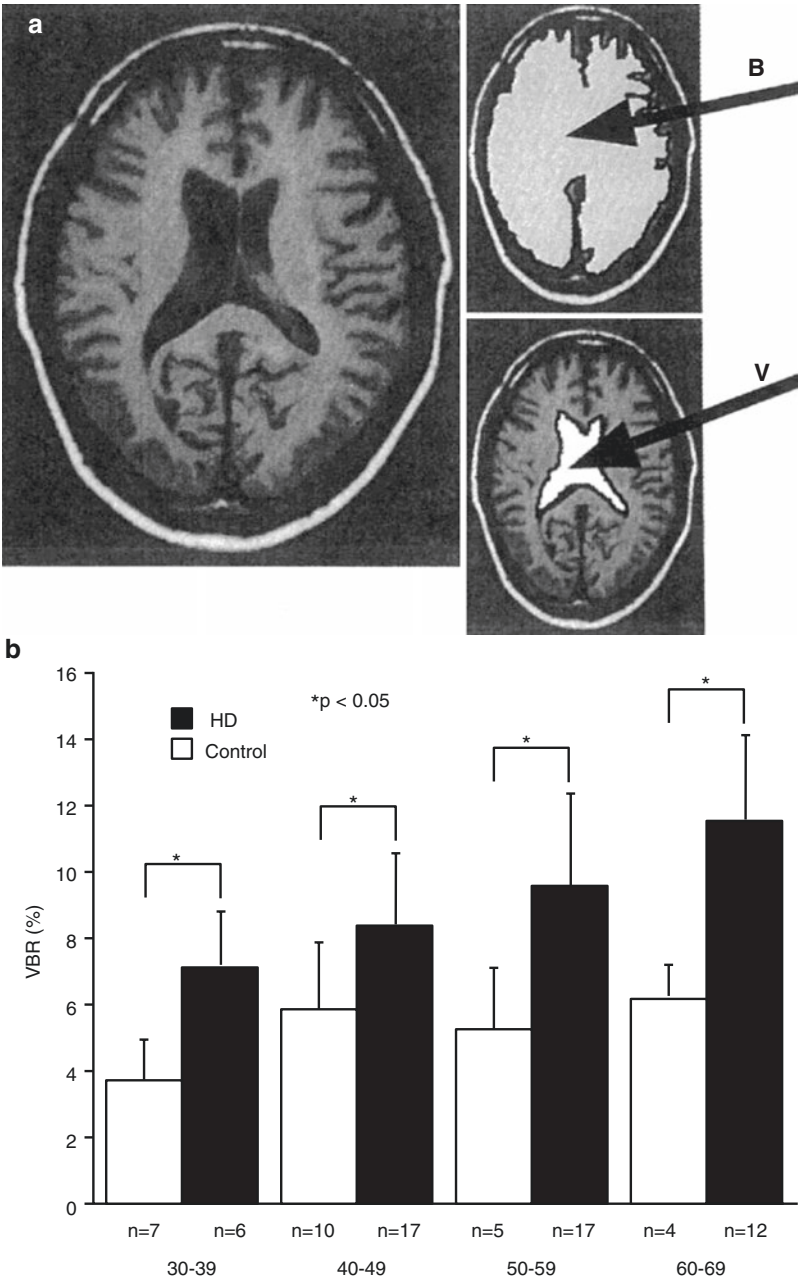

Fig. 13.1 Severe brain atrophy in hemodialysis patients compared to healthy individuals. (**a**) Planimetric outline of the ventricles and brain drawn on to the NIH images. To obtain the VBR, cross-sectional area of the lateral ventricle (V) is divided by the brain cross-sectional area (B). (**b**) VBR size of hemodialysis and controls according to age decades. All mean VBR values are higher in hemodialysis than controls (Student's *t* test, $P < 0.05$). *NIH* national institutes of health, *VBR* ventricular brain ratio. (Reproduced from [5])

It is supposed that hypotension during HD sessions might decrease brain blood flow and induce brain infarction, resulting in brain atrophy. Thus, we examined the role of HD-related hypotension in brain atrophy in patients on chronic HD using MRI. Frontal brain atrophy was assessed by the frontal atrophy index calculated by frontal brain area/intracranial frontal space as described previously [6]. The number of lacunae was also counted. We studied 32 HD patients without symptomatic neurological abnormalities or diabetes mellitus: male/female ratio 19/13; mean age 53 ± 10 (SD) years; and mean HD duration 11 ± 6 (SD) years. All dialysis-related hypotension episodes during the same period were identified from the medical records and counted. The results showed a positive association between the numbers of dialysis-related hypotension episodes, that is, a sudden drop in blood pressure during HD, was arbitrarily defined as a fall in systolic blood pressure >50 mmHg within 30 min of HD, associated with clinical symptoms such as fatigue, clouding of consciousness, muscle cramps, or other symptoms associated with hypoperfusion of the peripheral or central nervous system, identified from the medical records during 3 years with progression of frontal brain atrophy [7]. These results suggest that dialysis-related hypotension plays a role in progressive frontal lobe atrophy in HD patients.

13.2.2 Brain Atrophy in Patients Receiving PD

In patients receiving PD, unlike HD patients, a rapid decline in blood pressure and brain blood flow cannot occur. Therefore, there is a possibility that brain atrophy is less severe in PD patients than HD patients; however, little is known regarding brain atrophy in those patients. Therefore, we examined brain volume and its annual change over 2 years in PD patients. A recent analysis of brain MR images using the statistical parametric mapping (SPM) approach showed that gray matter volume decreases with aging, while white matter volume remains unchanged [8]. We analyzed brain MRI images of patients with NDD-CKD and those of patients undergoing PD using SPM to compare the brain volumes and percentage changes in brain volume between these two groups. T1-weighted magnetic resonance images were analyzed. Total gray matter volume (GMV), total white matter volume (WMV), and cerebrospinal fluid space volume were segmented, and each volume was quantified using statistical parametric mapping software. Normalized GMV (GMV ratio: GMR) and normalized WMV (WMV ratio: WMR) values were calculated by division of GMV and WMV by intracranial volume to adjust for variations in head size. We compared GMR and WMR between PD patients and patients with NDD-CKD in the cross-sectional study and the annual change in GMR between them in the longitudinal study.

An initial cross-sectional analysis in 69 patients with NDD-CKD (mean age 61 ± 10 years, 37 males and 32 females, estimated glomerular filtration rate [eGFR]: 39 ± 12 mL/min/1.73 m^2) and 62 patients undergoing PD (mean age 60 ± 12 years, 41 males and 21 females) with no history of cerebrovascular disease showed a significant inverse correlation between age and GMR, but not

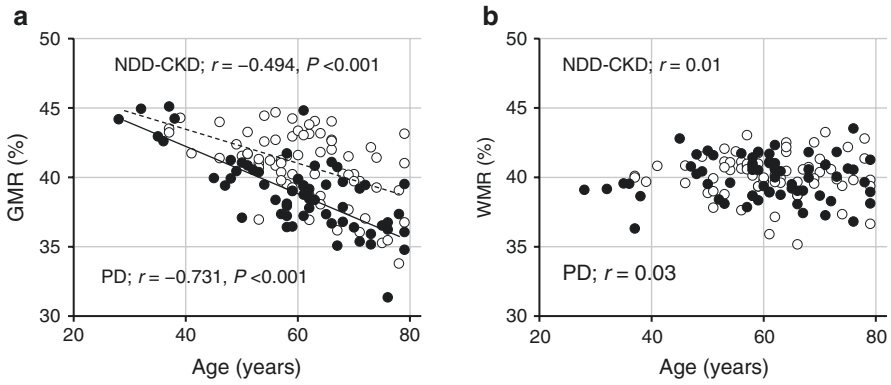

Fig. 13.2 Inverse association of GMR, but not WMR, with age. The association of the GMR and WMR with age in PD (closed circles; $n = 62$) and NDD-CKD patients (open circles; $n = 69$) are shown. GMRs, but not WMRs, are inversely associated with age in PD and NDD-CKD patients. *GMR* gray matter volume ratio, *NDD-CKD* non-dialysis-dependent chronic kidney disease, *PD* peritoneal dialysis, *WMR* white matter volume ratio. (Reproduced from [9])

WMR. In terms of the relationship between GMR and age, the regression line for PD patients was below that of NDD-CKD patients, meaning lower GMR in PD patients in the same age group, and the difference became larger with increasing age (Fig. 13.2) [9].

Next, when the annual change in GMR was compared between 61 NDD-CKD patients (mean age 61 ± 10 [SD] years, 32 males and 29 females, eGFR: 39 ± 12 [SD] mL/min/1.73 m^2) and 34 PD patients (mean age 60 ± 11 [SD] years, 21 males and 13 females) who underwent another brain MRI 2 years later, the least square mean (± SE) of the annual change in GMR was −0.38 ± 0.10% in NDD-CKD and −0.83 ± 0.14% in PD patients, indicating progression of brain atrophy to be faster, that is by a rate of more than twofold, in PD patients (Fig. 13.3) [9]. Given that the GMR in normal individuals decreases with age at a rate of 0.2–0.3%/year, as reported by Taki et al. [8], brain atrophy in PD patients progresses three times faster than that in normal individuals.

13.2.3 Association Between Brain Atrophy and Cognitive Function in CKD Patients

It is well known that cognitive impairment in patients with CKD is characterized by executive dysfunction, rather than memory dysfunction, although the precise mechanism of this remains to be elucidated. The trail making test (TMT) is commonly used to detect any decline in executive function due to frontal lobe dysfunction and yields three measures: TMT-A, TMT-B, and ΔTMT. The TMT-A test uses a dedicated form on which numbers from 1 to 25 are randomly located and measures the amount of time required for subjects to draw a line to connect the numbers in numerical orders. The TMT-B test uses a form on which numbers

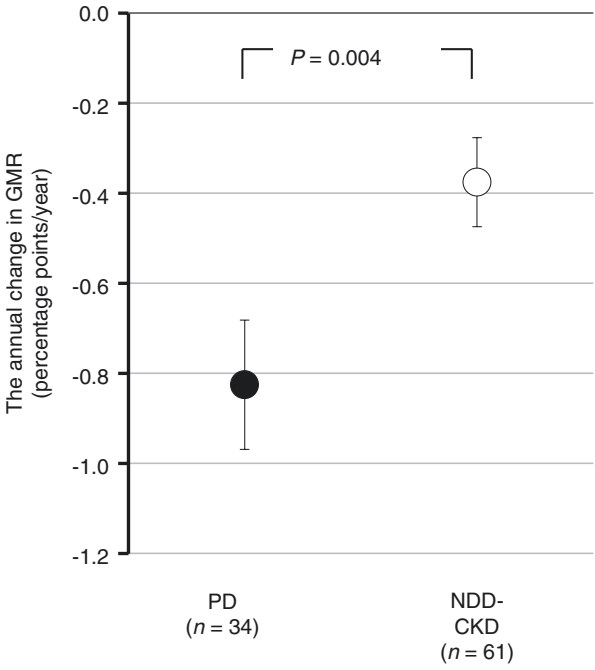

Fig. 13.3 Comparison of the annual change in GMR between PD and NDD-CKD patients. The annual change in GMR as determined by subtraction of the baseline GMR from the GMR after 2 years is significantly higher in PD patients than in NDD-CKD patients. Data are least square mean ± standard error, closed circles: PD patients, open circles: NDD-CKD patients. *GMR* gray matter volume ratio, *NDD-CKD* non-dialysis-dependent chronic kidney disease, *PD* peritoneal dialysis. (Reproduced from [9])

from 1 to 13 and Japanese kana characters from "a" to "shi" are randomly located and measures the amount of time required for subjects to draw a line to connect the numbers (in ascending order) and the kana characters (in the Japanese syllabary order) alternately. Finally, ΔTMT is defined as the difference between TMT-B and TMT-A.

Few reports are available regarding the relationship between brain atrophy and cognitive function. Thus, we performed brain MRI as well as conducting the TMT on 95 NDD-CKD patients with no history of cerebrovascular disease and assessed the correlation between GMR and TMT using multivariable regression analysis. The results showed that GMR was significantly inversely correlated to the scores of TMT-A, TMT-B, and ΔTMT. These correlations remained significant even after adjustment for confounding factors including age, sex, diabetes, eGFR, educational level, systolic blood pressure, smoking/drinking habits, hemoglobin level, history of cardiovascular disease, and urinary protein excretion (Table 13.1) [10].

We stratified the participants by eGFR (<45 vs. ≥45 mL/min/1.73 m^2) and examined the associations between GMR and TMT scores. Then, multivariable associations were observed in participants with eGFR <45 mL/min/1.73 m^2, but not in participants with eGFR ≥45 mL/min/1.73 m^2. According to this finding, it is considered that the correlation of brain atrophy with executive dysfunction is more robust in patients with severe renal dysfunction. Furthermore, when stratified by age (<65 vs. ≥65 years), multivariable associations were observed in participants ≥65 years, but not in participants <65 years. We suppose that the smaller GMR (more severe

Table 13.1 Univariable and multivariable-adjusted regression analyses of correlation between whole-brain GMR and TMT scores in all participants

		TMT-A	TMT-B	ΔTMT
Univariable analysis	*Standardized β*	−0.490	−0.516	−0.476
	P	<0.001	<0.001	<0.001
Model I	*Standardized β*	−0.442	−0.467	−0.432
	P	<0.001	<0.001	<0.001
Model II	*Standardized β*	−0.394	−0.423	−0.393
	P	0.002	<0.001	0.003
Model III	*Standardized β*	−0.349	−0.362	−0.332
	P	0.012	0.006	0.013

GMR gray matter volume ratio, *TMT* trail making test
Model I: Multivariable analysis adjusted for sex and age. Model II: Model I + diabetes mellitus, estimated glomerular filtration rate, and education. Model III: Model II + systolic blood pressure, smoking habits, drinking habits, hemoglobin, previous history of cardiovascular disease, and log-transformed urinary protein to creatinine ratio

brain atrophy) and the higher TMT scores (more severe executive dysfunction) in the elderly compared with younger participants might attribute to the more robust association between them in the elderly probably due to the threshold effect reported in the neuropsychological correlates of white matter lesions in healthy elderly subjects [11].

We then divided the brain into four regions, that is, the frontal, temporal, parietal, and occipital lobes, and examined whether GMR correlated with TMT-A, TMT-B, and/or ΔTMT in each of these regions. Interestingly, significant inverse correlations were observed after multivariable adjustment in the frontal and temporal lobes, but not in the parietal and occipital lobes [10]. These findings suggested that atrophy of the frontal and temporal lobes affects frontal lobe function (i.e., executive function), which was consistent with our hypothesis.

13.2.4 Factors Associated with Cognitive Impairment

Although the mechanisms by which CKD leads to cognitive and functional decline are still not fully elucidated, various factors are believed to be involved in the pathogenesis of cognitive impairment in CKD [12], including vascular risk factors, such as cerebrovascular disorder, hypertension, diabetes, dyslipidemia, myocardial infarction, atrial fibrillation, and smoking habits [13, 14] as well as in the general population [15–21].

Nonvascular risk factors such as anemia, albumin, education, level of physical, social, and mentally stimulating activities, and depressive symptoms are also documented to be important risk factors for cognitive impairment and dementia [22–29] and are also frequently present in patients with CKD. Other nontraditional vascular factors and nonvascular factors such as hemostatic and coagulation abnormalities, inflammatory cytokines, oxidative stress, hyperhomocysteinemia,

and hyperparathyroidism [4, 30–33] may also explain the greater risk of cognitive impairment and dementia in individuals with CKD.

13.2.4.1 Anemia

Despite the lack of clinically apparent neurological symptoms or morphological abnormalities, patients with CKD accompanied by anemia present with impairment in cerebral blood flow (CBF) and oxygen metabolism, which is reportedly prominent in the frontal cortex [34–36]. Meanwhile, renal anemia correction with recombinant human erythropoietin (rHuEPO) has been shown to improve brain function. Using the Wechsler Adult Intelligence Scale (WAIS), Temple et al. [37] reported that brain function was significantly improved by correction of anemia with rHuEPO therapy (hemoglobin 5.8 g/dL → 9.3 g/dL) in nine patients of the treatment group, but not in the nine control patients matched with the treatment group for age, educational status, and social class, who did not receive rHuEPO. Grimm et al. [38] measured event-related EEG potentials (P300) of the brain, stimulus-related evoked potentials, in 15 patients undergoing chronic HD and found that anemia correction with rHuEPO therapy from a hematocrit of 22.7%–30.6% significantly decreased P300 peak latency and improved higher brain function (Fig. 13.4). P300 is considered to be potentially associated with intellectual information processing, such as stimulus perception, discrimination, and task execution, whereas its peak latency is an indicator of stimulus evaluation time in intracerebral information processing. P300 latency is reportedly prolonged with aging and neurological diseases, and it is also known to be markedly prolonged particularly in patients with dementia. In addition, P300 latency has been shown to correlate with scores of general

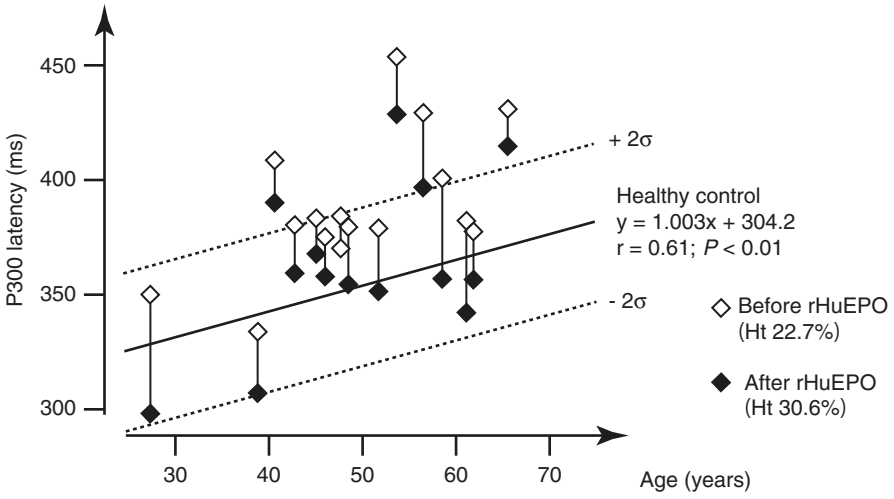

Fig. 13.4 Effect of anemia correction on cognitive impairment evaluated by P300 latency. In 15 patients undergoing chronic hemodialysis, after the start of rHuEPO therapy (4.7 ± 1.2 months), P300 peak latency significantly decreased as anemia was corrected (hematocrit, 22.7% → 30.6%). *rHuEPO* recombinant human erythropoietin. (Reproduced from Ref. [38])

intellectual functioning tests, such as Mini-Mental State Examination (MMSE) and the revised Hasegawa dementia scale, and with CBF. Moreover, although P300 latency is prolonged in some individuals without neurological abnormalities but with almost normal intellectual function, P300 latency may be used to detect early-stage dementia or latent cognitive impairment. These results indicate that anemia makes a reversible contribution to uremic cognitive dysfunction.

13.2.4.2 Albuminuria and Decreased Kidney Function

The relationship between CKD and dementia was investigated in the Hisayama Study. Takae et al. [39] investigated the association between albuminuria and the development of dementia based on the results of a follow-up study in the residents of the town of Hisayama in Fukuoka Prefecture, Japan. Of all the residents ≥60 years of age who underwent the health screening program for elderly residents of the town in 2002, 1562 community-dwelling Japanese subjects aged ≥60 years without dementia were followed up for 10 years, and the association between the urinary albumin/creatinine ratio (UACR) and dementia development was examined using the Cox proportional hazards model. UACR was categorized as normoalbuminuria (UACR <30 mg/g) and albuminuria (UACR ≥30 mg/g), and UACR in the normoalbuminuria range was further divided into the following tertile categories: low-normal (≤6.9 mg/g), medium-normal (7.0–12.7 mg/g), and high-normal (12.8–29.9 mg/g). After multivariable adjustment, the incidence of all-cause dementia rose significantly with increasing UACR, with the hazard ratios for all-cause dementia being 1.12 (95% CI, 0.78–1.60), 1.65 (1.18–2.30), and 1.56 (1.11–2.19) in those with UACR of 7.0–12.7 mg/g, 12.8–29.9 mg/g, and ≥ 30.0 mg/g, respectively, as compared with subjects with UACR of ≤6.9 mg/g. When the outcome was divided by the type of dementia, that is, Alzheimer's disease and vascular dementia, the risk for both types of dementia rose significantly with increasing UACR, with the hazard ratios for the development of Alzheimer's disease being 1.20 (95% CI, 0.77–1.86), 1.75 (1.16–2.64), and 1.58 (1.03–2.41), and the hazard ratios for the development of vascular dementia being 1.03 (0.46–2.29), 1.94 (0.96–3.95), and 2.19 (1.09–4.38) in those with UACR of 7.0–12.7 mg/g, 12.8–29.9 mg/g, and ≥ 30.0 mg/g, respectively, as compared with subjects with UACR of ≤6.9 mg/g. In terms of the relationship between kidney function and dementia, a significant increase in the risk of vascular dementia was observed in patients with an eGFR of <60 mL/min/1.73 m^2, while no such association was observed for Alzheimer's dementia.

13.2.4.3 Oxidative Stress

To elucidate the mechanism of cognitive impairment development in CKD, we conducted the following experiment using 5/6 nephrectomized CKD mice [40]. Working memory performance was tested by the radial arm water maze test. We examined the working memory test and histological examination of mouse brains after 4 and 8 weeks. Next, we investigated the effect of tempol (TMP) against uremia-induced neurodegeneration and oxidative stress in the mouse brain. Eight weeks after CKD induction, vehicle-treated mice made significantly more errors than sham-operated

control mice, while TMP improved working memory performance in CKD mice (Fig. 13.5). CKD was associated with accumulation of 8-hydroxy-2′-deoxyguanosine (8-OHdG) in the hippocampal neuronal cells, but not in TMP-treated CKD mice. The numbers of pyknotic neuronal cells were increased in the hippocampus of CKD mice at 8 weeks, but not in CKD mice treated with TMP. According to these findings, we concluded that uremia is associated with spatial working memory dysfunction in mice and that treatment with TMP protects against cerebral oxidative stress and improves cognitive dysfunction in uremic mice, suggesting their potential usefulness for the treatment of cognitive dysfunction in uremia. These results suggest the involvement of CKD-induced oxidative stress as the primary cause of neuronal cell damage and decreased learning function in CKD.

13.2.4.4 Renin-Angiotensin System

The source of oxidative stress was considered to be uremic toxins, but this remains unclear. Thus, we examined whether the brain renin-angiotensin system was activated in the CKD mouse model, and whether it contributed to cognitive impairment [41]. Errors in the radial arm water maze test were significantly increased in the untreated CKD mice, but were not increased in the CKD mice treated with telmisartan. Tissue brain AII concentrations, accumulation of 8-OHdG and lipid peroxidation in the brain, and the appearance of pyknotic cells were also increased in the untreated CKD mice, but not in the CKD mice treated with telmisartan. These results suggest the involvement of the renin-angiotensin system in oxidative stress production in the brains of CKD mice. It is noteworthy that the dose of telmisartan used in this experiment was comparable to the regular clinical dose. A meta-analysis also demonstrated the inhibitory effect of renin-angiotensin system inhibitors on cognitive impairment associated with Alzheimer's disease or aging in clinical practice [42], suggesting a promising effect of these agents for the prevention of cognitive impairment in CKD.

13.2.4.5 Uremic Toxins

The higher incidence of cognitive impairment in patients with end-stage kidney disease has been attributed to both vascular causes and neurodegenerative causes due to progressive accumulation of uremic toxins [2]. Several studies have attempted to treat cognitive impairment by targeting uremic toxins. Nocturnal daily HD improved CI symptoms, such as psychomotor efficiency, attention, and working memory, in a small longitudinal pilot study [43]. Longer dialysis sessions have also been suggested to improve cognitive function. Ok et al. [44] followed up 247 patients who consented to receive 8-h dialysis therapy three times per week; the control group was matched for age, sex, diabetic status, and dialysis vintage (receiving 4-h dialysis therapy three times per week) for 12 months, and their outcomes, cognitive function, quality of life, and so on, were compared. They reported that the capacity to memorize was significantly improved in patients receiving longer dialysis session length. However, some other studies showed that more intensive dialysis with a more effective clearance of uremic solutes, that is, six times per week, has not been found effective in improving cognitive function [45, 46].

Because serum levels of uremic toxins are remarkably decreased after kidney transplantation [47], it is considered that cognitive function in posttransplant

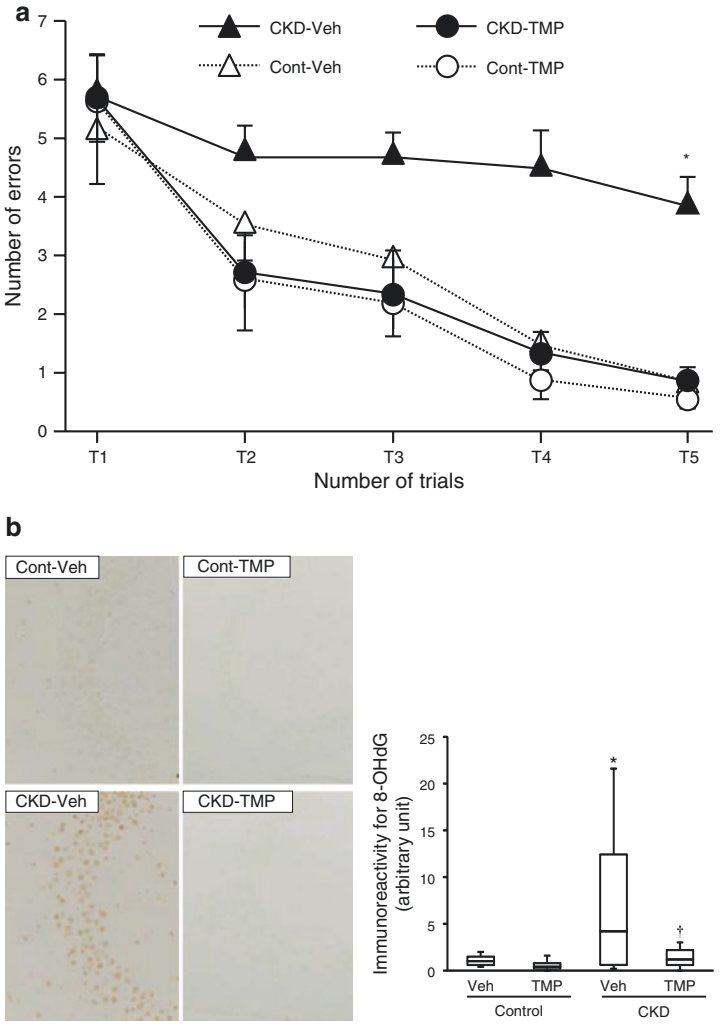

Fig. 13.5 Effect of tempol on prevention of uremia-induced spatial working memory dysfunction and inhibition of 8-OHdG accumulation in the hippocampal CA3 region. (**a**) The numbers of errors during radial arm water maze test on the fifth day in Cont-Veh (white triangle), CKD-Veh (black triangle), Cont-TMP (white circle), and CKD-TMP (black circle) mice are shown. The number of errors in CKD-TMP mice is significantly decreased to levels similar to those observed in control mice, and significantly lower than CKD-Veh mice. The ends of the box represent the upper and lower quartiles; thus, the box spans the interquartile range. The median is marked by a vertical line inside the box. The two lines outside the box that extend to the highest and lowest observations represent the whiskers. $^{*}P < 0.05$ versus the other three groups. (**b**) Effect of TMP on prevention of oxidative DNA damage generation. Representative microphotographs of 8-OHdG immunostaining in the hippocampal CA3 region from each group are shown. Magnification: 200×. Quantitative analysis of 8-OHdG-positive neurons in the hippocampal CA3 region is shown. 8-OHdG immunoreactivity in the hippocampal CA3 region is significantly higher in CKD-Veh mice than TMP-treated CKD mice. The ends of the box represent the upper and lower quartiles; thus, the box spans the interquartile range. The median is marked by a vertical line inside the box. The two lines outside the box that extend to the highest and lowest observations represent the whiskers. $^{*}P < 0.05$ versus Cont-Veh mice. $^{\dagger}P < 0.05$ versus CKD-Veh mice. *CA3* cornu ammonis 3, *CKD* chronic kidney disease, *Cont* control, *8-OHdG* 8-hydroxydeoxyguanosine, *TMP* tempol, *Veh* vehicle. (Reproduced from [40])

patients is superior to that in dialysis patients. Indeed, a significant improvement in cognitive function, including attention, memory, executive functions, the pace of data processing, and language functions, was reported in CKD patients after kidney transplantation [48–55]. Harciarek et al. [49] reported that a kidney transplant was associated with improved neuropsychological performance in patients with end-stage kidney disease. It was reported that the early beneficial effects of transplantation on cognitive function were not transient and were still evident after 1 year following transplantation [49, 50].

13.2.5 Dialysis Modalities and Cognitive Impairment

Association between dialysis modalities and cognitive impairment has also been pointed out. Wolfgram et al. [56] compared the incidence of dementia between 112,960 patients undergoing HD and 8663 patients undergoing PD and reported that the incidence was significantly lower in patients undergoing PD and remained significantly lower even after adjustment in the multivariate analysis, while the significant difference was maintained after propensity score matching. A meta-analysis O'Lone et al. [57] revealed that cognitive function was insignificantly better in patients undergoing PD. Recently, Tian et al. [58] conducted a meta-analysis of 15 cohort or cross-sectional studies, comparing the cognitive functions using neuropsychological tests and covering the executive function, memory, orientation, attention, etc. By qualitative analysis, it showed that more studies are inclined to PD compared with HD with better cognitive functions. By quantitative analysis, PD showed better performance in the tests of MMSE, Montreal Cognitive Assessment (MoCA), and Stroop interference test and exhibited lower risk of dementia compared with HD.

13.3 Association Between Frailty and Cognitive Impairment

Frailty is a common geriatric syndrome that embodies an elevated risk of catastrophic declines in health and function among older adults. This state was initially described and validated by Fried et al. [59] in a geriatric population but is emerging as an important risk factor in patients with CKD.

13.3.1 Non-CKD Patients

Frailty has been associated with poor cognitive function, cognitive decline, and dementia in older adults without kidney disease. Current evidence in the literature from cross-sectional and longitudinal studies has shown relationships between frailty and cognitive disorders.

Recently, several systematic reviews and meta-analyses of observational, cohort, and cross-sectional studies on the association of frailty with cognitive impairment

were performed and reported [60–62]. To analyze the relationship between cognition and frailty in the elderly, Brigola et al. [60] performed a systematic review on the currently existing literature concerning the subject was carried out. A total of 19 studies were selected for review, from which 10 were cross sectional and 9 longitudinal. There was a relationship between components of frailty and the cognitive domains. Risk of mild cognitive impairment (MCI), dementia, and mortality were all evidenced in the relationship between frailty and cognitive impairment. According to the results of the reviewed studies, the authors illustrated a model of association between factors, frailty, cognitive impairment, and their outcomes in older adults in order to better understand the frailty-associated factors (Fig. 13.6). Furtado et al. [61] also performed a systematic review of prospective studies published from 2000 to 2017 to analyze the magnitude of the effect size of the cognitive status of populations over 60 years of age, when comparing nonfrail versus prefrail and nonfrail versus frail subgroups. After applying additional search criteria, 14 studies (26,798 old participants) were selected. When comparing the scores of

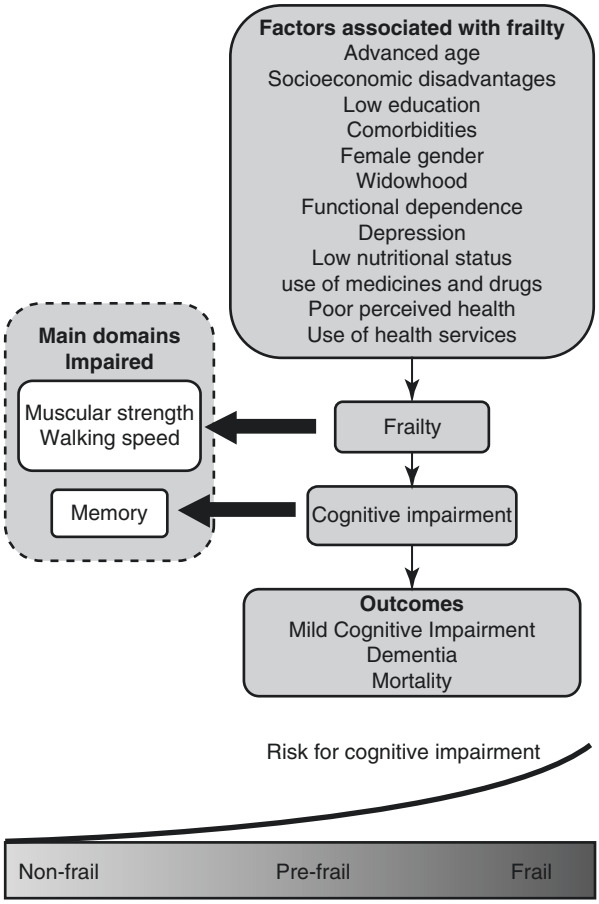

Fig. 13.6 Model of association between factors, frailty, cognitive impairment, and their outcomes in older adults. (Reproduced from Ref. [60])

cognitive status (MMSE score) of the participants who were nonfrail versus prefrail and nonfrail versus frail subgroups, significant statistical differences were found for both comparisons. More recently, Borges et al. [62] examined the risk of cognitive disorders associated with physical frailty in older adults from community-based studies using a systematic review and meta-analysis of cohort and longitudinal studies, which assessed dementia and cognitive impairment as a primary or secondary outcome. The results showed that baseline frailty was significantly associated with an increased risk of geriatric cognitive disorders.

Handgrip strength is an easy, noninvasive, and inexpensive measure of muscle strength in the elderly, which has been reported to be well correlated with the muscle strength of limbs and the human trunk [63, 64]. Weak handgrip strength is a risk factor for disability, morbidity, and mortality and is central to the definitions of sarcopenia and frailty [65, 66]. The measurement of handgrip strength may be especially useful in the context of multimorbidity to identify patients at high risk of adverse outcomes, who may benefit from closer clinical attention [67]. Recently, the association between decline in handgrip strength and development of dementia was examined in the Hisayama Study. Hatabe et al. [68] estimated the risk conferred by a decline in handgrip strength over a 15-year period on the development of dementia using a Cox proportional hazards model. A total of 1055 Japanese community dwellers without dementia aged 60–79 years were followed for 24 years; 835 of them had participated in a health examination in 1973–1974 (mean age, 53 years). The age- and sex-adjusted incidence of total dementia increased significantly with greater decline in handgrip strength. A greater decline in handgrip strength was significantly associated with higher risk of total dementia after adjusting for potential confounding factors; subjects with severely decreased handgrip strength had 1.51-fold increased risk of total dementia compared to those with increased or unchanged handgrip strength.

13.3.2 CKD Patients

The association between frailty and cognitive impairment has also been reported in CKD patients including NDD-CKD and dialysis patients and also in kidney transplant patients [69–75].

13.3.2.1 NDD-CKD Patients

To evaluate the prevalence of MCI and the relationship between MCI and physical function among older adults with predialysis CKD, Otobe et al. [69] conducted a cross-sectional study of 120 patients, aged ≥65 years, with NDD-CKD without dementia. Physical, clinical, and biochemical parameters were compared between normal and MCI patients using the Japanese version of the MoCA-J. Logistic and linear regression analyses showed gait speed was significantly associated with MCI even after adjustment for multivariable covariates. They also conducted a 2-year prospective cohort study enrolling 131 patients ≥65 years with non-dialysis-dependent CKD who were classified into four groups: patients with mild-to-moderate (eGFR

≥30 mL/min per 1.73 m^2) or severe (eGFR <30 mL/min per 1.73 m^2) CKD and high (handgrip strength ≥26 for men and ≥18 kgf for women and gait speed ≥0.8 m/s) or low (handgrip strength <26 for men and <18 kgf for women and/or gait speed <0.8 m/s) physical function [70]. Multivariate logistic regression analysis showed that the combination of severe CKD and low physical function was significantly associated with cognitive decline defined as a %MoCA-J value in the lowest quartile (a %MoCA-J of <92%), although no significant cognitive decline was observed in patients with either severe CKD or low physical function alone.

Coppolino et al. [71] examined the entity of functional, general health and cognitive impairment and the possible relationship between these types of dysfunction and the severity of renal impairment in a series of frail individuals with nonadvanced CKD. Among 2229 geriatric subjects, 271 subjects (162 women and 109 men) were diagnosed as frail and CKD. Cognitive capacities significantly decreased across CKD stages (P for trend <0.0001). In fully adjusted multivariate analyses, cognitive status remained an independent predictor of eGFR ($\beta = 0.465$; $P < 0.0001$). The authors conclude that mild-to-moderate CKD is highly pervasive among frail elderly individuals, and the severity of renal dysfunction is independently correlated with that of cognitive impairment.

13.3.2.2 HD Patients

To investigate whether frailty is associated with poor cognitive function in adults of all ages undergoing HD, McAdams-DeMarco et al. [72] conducted a longitudinal cohort study using 324 adult incident HD patients. At HD initiation, the patients were classified into three groups (frail, intermediately frail, and nonfrail) based on the Fried frailty phenotype, and global cognitive function (modified mini-mental state [3MS]) and speed/attention (TMT-A and TMT-B) were assessed at cohort entry and 1-year follow-up. The results showed that frailty was independently associated with lower cognitive function at cohort entry for all three measures and with worse 3MS at 1-year follow-up. To examine the relationships between patient-reported (subjective) and objective cognitive functioning and everyday functioning of dialysis patients, Song et al. [73] performed a longitudinal observational study in 135 patients who completed a telephone-based neuropsychological battery (Brief Test of Adult Cognition by Telephone, a measure of objective cognitive functioning), subjective cognitive functioning (Patient's Assessment of Own Functioning Inventory), and everyday functioning. Multivariate logistic regression models showed subjective, but not objective, cognitive functioning was a significant predictor of everyday functioning. The authors concluded that the study findings point to the importance of assessing patients' subjective cognitive functioning, not as a stand-alone screening tool, but to optimize clinical assessment and management.

13.3.2.3 PD Patients

The association between frailty and cognitive impairment has not been reported in patients on PD until recently. However, more recently, Yi et al. [74] investigated the prevalence of coexisting frailty and cognitive impairment and its association with clinical outcomes in 784 patients on PD. The authors demonstrated that patients

with cognitive impairment were more than those with frailty (55.5% vs. 27.6%), clinical frailty scale was negatively associated with MoCA score, and coexisting frailty and cognitive impairment decreased patient survival rate and increased peritonitis rate.

13.3.2.4 Kidney Transplant Patients

It is considered that restoration of kidney function after kidney transplant generally improves cognitive function, but it is unclear whether frail recipients achieve such cognitive improvements as same as nonfrail ones. To investigate potential short- and medium-term effects of frailty on posttransplant cognitive trajectories, Chu et al. [75] compared posttransplant cognitive function assessed by 3MS between 100 frail and 565 nonfrail recipients aged ≥18 years old using a mixed effects model with random slope (time) and intercept (person) up to 4 years posttransplant. Although both recipients experienced short-term cognitive improvement up to 3 months, improvements plateaued among nonfrail recipients, whereas cognitive function declined among frail recipients between 1 and 4 years. Finally, cognitive scores were significantly lower for frail recipients compared with nonfrail recipients after 4 years of kidney transplantation.

13.3.3 Mechanism of the Association of Frailty with Cognitive Impairment

A number of traditional and nontraditional vascular factors and nonvascular factors are strongly implicated in the pathophysiological relationship between renal dysfunction and cognitive decline and frailty [76]. When considering the mechanism of the association of frailty with cognitive impairment, it seems better to consider the mechanism of protective influence of physical activity on cognitive impairment. Several possible mechanisms may underlie the protective influence of physical activity on the risk of dementia. Several recent randomized controlled trials (RCTs) of elderly individuals without dementia have demonstrated that exercise training increased brain volume and improved cognitive function [77–79].

Experimental studies using amyloid precursor protein-overexpressing transgenic mice have shown that exercise decreased the amount of β-amyloid (Aβ) oligomers in addition to depositing Aβ in the brain [5, 42, 74]. Liang et al. [80] have also reported that among 69 older adults with normal cognitive function, physically active individuals who met or exceeded the exercise recommended by American Heart Association had significantly lower levels of Aβ deposition measured with positron emission tomography and higher levels of $A\beta_{42}$ in the cerebrospinal fluid compared with inactive individuals who did not meet the recommendation. Alternatively, some other animal studies have demonstrated that physical training increases angiogenesis, synaptogenesis, and neurogenesis,

especially in hippocampus and in gyrus dentatus, and initiates the upregulation of numerous neurotrophic factors in the brain [81, 82], especially in hippocampus [83, 84].

Another important mechanism which explains the effect of physical exercise on cognition includes an endogenous substance which plays a central role in the health status of neurons and called brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophic growth factor that plays an important role in maturation, synaptic connection, neuronal repair, and plasticity of the central nervous system [85, 86]. An increase in BDNF concentrations is associated with an increase in hippocampal size and an improvement in the performance of spatial memory and learning [87]. Insulin-like growth factor-1 (IGF-1) is shown to increase BDNF signaling in response to activity stimulation. Exercise-induced neurogenesis in the rat hippocampus is inhibited following injection of a serum that blocks IGF-1 from leaving the bloodstream and entering the cerebrospinal fluid [88]. IGF-1 also contributes greatly to the exercise-induced effects of BDNF on recall [89]. Neuronal uptake of IGF-1 is stimulated by exercise, and these neurons then show signs of activity and increase their expression of BDNF [90].

13.4 Effect of Exercise on Cognitive Function

13.4.1 Non-CKD Patients

Physical activity has a promising role in delaying cognitive impairment in general population [91]. A lot of clinical studies have shown that exercise intervention has a beneficial role in improving cognition in healthy elderly participants with and without MCI [78, 79, 92–103]. Lautenschlager et al. [103] conducted an RCT of a 24-week physical activity intervention in 138 participants aged 50 years or older who reported memory problems but did not meet criteria for dementia. Participants were randomly allocated to an education and usual care group or to a 24-week home-based program of physical activity. Cognitive function was modestly improved in participants in the intervention group, whereas was deteriorated in the usual care group. Shimada et al. [79] conducted a single-blind RCT in a population-based study of participants and evaluated 945 adults 65 years or older with MCI, enrolled 308, and randomly assigned them to the combined activity group in which subjects underwent weekly 90-min sessions focused on physical and cognitive activities including aerobic exercise, muscle strength training, postural balance retraining, and dual-task training (n = 154) or the health education control group (n = 154) for 40 weeks. Compared with the control group, the combined activity group showed significantly greater scores on the MMSE and Wechsler Memory Scale-Revised-Logical Memory II.

However, several studies [104–107] have reported no improvement in cognitive function by physical exercise. Thus, Cai et al. [108] conducted a meta-analysis and systematic review of RCTs that evaluated the effect of exercise on cognitive function compared with control group for people with chronic diseases (e.g., arthritis, asthma, cancer, chronic obstructive pulmonary disease, diabetes, heart disease, or acquired immunodeficiency syndrome) in 35 studies with 3113 participants. The main analysis revealed a positive overall random effect of exercise intervention on cognitive

function in patients with chronic diseases, and the secondary analysis revealed that aerobic exercise interventions, but not resistance exercise interventions, had a positive effect on cognition in patients with chronic diseases. Northey et al. [109] also performed a systematic review with multilevel meta-analysis of the randomized controlled trials of physical exercise interventions in community-dwelling adults >50 years, with an outcome measure of cognitive function to examine the effects of a multicomponent exercise program on the cognitive function of older adults with amnestic MCI. Analysis of 333 dependent effect sizes from 36 studies showed that physical exercise interventions including aerobic exercise, resistance training, multicomponent training, and tai chi improved cognitive function. Exercise appears to prevent brain atrophy or even increase hippocampal volume in the general population [77, 78]. To examine whether aerobic fitness training of older humans can increase brain volume in regions associated with age-related decline in both brain structure and cognition, Colcombe et al. [77] conducted an RCT in 59 healthy, but sedentary community-dwelling volunteers, aged 60–79 years. Half of the older adults served in the aerobic training group, the other half of the older adults participated in the toning and stretching control group. High spatial resolution estimates of gray and white matter volume, derived from 3D spoiled gradient recalled acquisition MRI images, were collected before and after the 6-month fitness intervention. The results showed that significant increases in brain volume, in both gray and white matter regions, were found as a function of fitness training for the older adults who participated in the aerobic fitness training, but not for the older adults who participated in the stretching and toning (nonaerobic) control group, suggesting that cardiovascular fitness is associated with the sparing of brain tissue in aging humans.

Erickson et al. [78] performed a single-blind RCT in which 120 older adults were randomly assigned to receive either moderate-intensity aerobic exercise 3 day/week or stretching and toning exercises that served as a control. Exercise training increased hippocampal volume by 2%, effectively reversing age-related loss in volume by 1–2 years. Hippocampal volume declined in the control group, but higher physical fitness partially attenuated the decline, suggesting that aerobic exercise training is effective at reversing hippocampal volume loss in late adulthood, which is accompanied by improved memory function. According to these findings, the authors concluded that aerobic exercise is neuroprotective and starting an exercise regimen later in life is not futile for either enhancing cognition or augmenting brain volume. A recent RCT [79] also demonstrated the effect of combined activity against left medial temporal lobe atrophy.

13.4.2 CKD Patients

It is conceivable that physical activity and fitness levels are related to cognitive function in patients with chronic kidney disease, but there have been limited studies in this area. In a study by Parsons et al. [110] using the Kidney Disease Quality of Life (KDQOL) questionnaire, no changes in cognitive function score were found in patients on HD who attended a 5-month intradialytic aerobic exercise program three

times a week (cycle ergometer and mini-stepper) for 30 min in each of the first 2 h of HD, while increased physical performance was found. It is considered that the use of inappropriate instrument for assessing cognitive function and the low-intensity intradialytic exercise training seem to be the main reasons for the luck of changes in parameters related to cognitive function [111]. Meanwhile, Martins et al. [112] compared cognitive function assessed by 3MS between 37 inactive patients and 49 patients participating physical performance program for at least 3 months. The exercise training program consisted of two weekly 20- to 30-min sessions of combined strengthening and peripheral muscle resistance exercises and stretching performed before the initialization of the HD sessions and lasted 6 months. The results showed that better cognitive function was observed in active patients as compared to the inactive ones. According to the results, the authors concluded that patients with better cognitive responses are more physically active and/or physical activity contributes to better cognitive function. Unfortunately, however, this study was not an RCT, and the 3MS is not a sensitive measure for change in global cognition, which limits any conclusions.

Recently, this effect has been evaluated by RCTs [113–115]. Manfredini et al. [113] conducted a multicenter RCT, EXCITE trial, in which, cognitive function and quality of life (QOL) were evaluated by KDQOL-SF in addition to the physical performance to examine whether a simple, personalized walking exercise program at home improves functional status in adult patients on dialysis. A total of 296 patients were randomized to normal physical activity (control; $n = 145$) or walking exercise ($n = 151$). The results showed that the cognitive function score and QOL, as well the physical performance, were improved significantly in the exercise arm compared with the control arm. Baggetta et al. [114] reanalyzed the data of the EXCITE trial to elucidate whether physical exercise program improves physical and cognitive function in elderly HD patients. In this study, 115 patients of the EXCITE trial aged >65 years (active arm, $n = 53$; control arm, $n = 62$) were submitted in random order to a home-based, low-intensity physical exercise program. The cognitive function dimension of QOL significantly reduced in the control arm ($P = 0.04$), while it remained unchanged in the active arm ($P = 0.78$) (between groups difference $P = 0.05$). This secondary analysis of the EXCITE trial shows that a home-based, exercise program improves physical and cognitive performance and is well tolerated in elderly HD patients. McAdams-DeMarco et al. [115] conducted a pilot RCT of 20 HD patients to study the impact of 3 months of intradialytic cognitive training (tablet-based brain games), exercise training (foot peddlers), or standard care on cognitive function. Patients with standard care experienced a decrease in psychomotor speed and executive function, assessed by TMT-A, TMT-B, and ΔTMT, while this decline was not seen among those with cognitive training or exercise training (Fig. 13.7).

As a mechanism of the effect of exercise training on the improvement of cognitive function in HD patients, an increase in cerebral blood flow has been suggested [116]. A pilot RCT was conducted to evaluate the effect of intradialytic aerobic training on cerebral blood flow and cognitive impairment in HD. Cognitive function and blood flow velocity were compared between 15 patients who underwent intradialytic aerobic training three times a week for 4 months with another 15 control patients. Trained

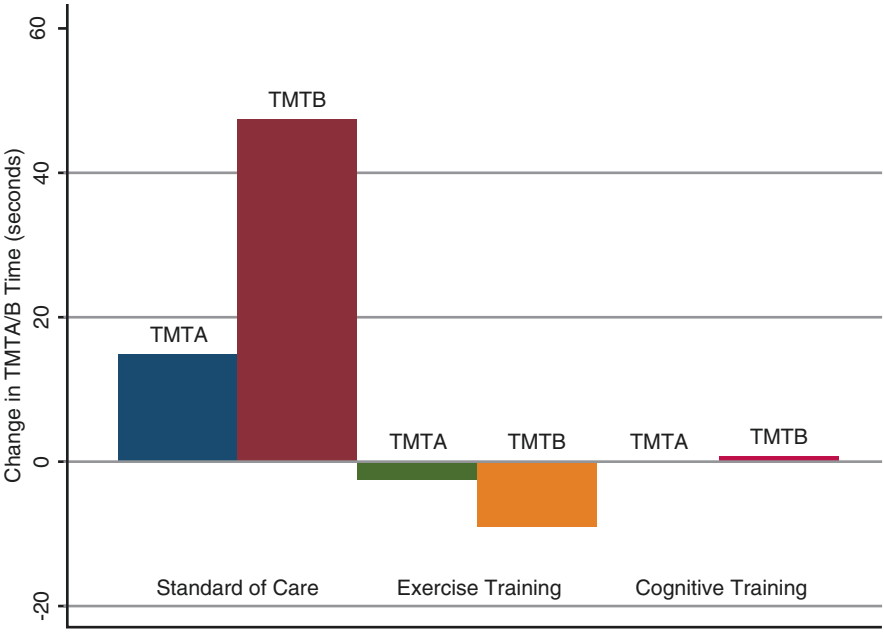

Fig. 13.7 Mean change in psychomotor speed (TMT-A and TMT-B) at 3 months for those with cognitive training, exercise training, and standard of care. *TMT* trail making test. (Reproduced from [115])

patients had a statistically significant improvement of cognitive impairment and basilar maximum blood flow velocity. Intradialytic aerobic training improved cognitive impairment and cerebral blood flow of patients in HD, suggesting a possible mechanism improving cognitive impairment by physical training in HD [116].

13.5 Conclusion

Frailty and cognitive impairment are both highly prevalent in CKD patients and are associated with each other. Both conditions have been identified as incremental risk factors for mortality and when they coexist, the risk is higher than when either of them exists alone. Physical exercise training is reported to be effective in preventing and treating both frailty and cognitive impairment, and thus should be implemented in the elderly CKD patients.

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