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Risk factors for cognitive dysfunction in CKD and hypertensive subjects

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Abstract
Purpose Cognitive dysfunction (CO/DY) in chronic kidney disease (CKD) patients has long been recognized. Hypertension is also associated with CO/DY. The study describes associated factors with CO/DY in CKD patients compared to hypertensive subjects.
Methods Ninety-six hypertensive subjects without CKD, 19 patients with CKD stages I–II, 33 with CKD III, 42 with CKD stage IV, 33 on hemodialysis (HD) and 33 on peritoneal dialysis (PD) were included in our study. Cognitive impairment measured by MMSE, clock-drawing test and IADL was considered as primary outcome.
Results In all groups tested, age was significantly associated with CO/DY by almost all cognitive function tests. Among CKD patients, CKD stage and DM were significantly associated with CO/DY by all three cognitive function tests. PTH levels were also associated with CO/DY by MMSE and clock-drawing tests. In hypertensives, pulse pressure (PP) was associated with CO/DY by clock-drawing and IADL tests, while those receiving CCBs as monotherapy were less likely to have CO/DY by IADL test. For dialysis patients, DM was significantly related to CO/DY by MMSE and clock-drawing tests. In the same group of patients Hb <11 g/dl was significantly correlated with CO/DY by MMSE, dialysis modality and Kt/V >1.2 by IADL test. PD patients were less likely to present with CO/DY by clock-drawing test.
Conclusions In every CKD stage, the risk of CO/DY increased significantly. Low Hb levels (Hb <11 g/dl) and increased serum PTH levels were associated with CO/DY while DM plays also a significant role in cognitive function deterioration. Among hypertensive subjects, those with PP ≤60 mmHg or receiving CCBs showed a better executive function.

Keywords Cognitive dysfunction · Cognitive testing · CKD · Hypertensive subjects

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Introduction

Cognitive dysfunction (CO/DY) has long been recognized as a complication of chronic kidney disease (CKD) [1]. Its prevalence is more than double compared to the general population [2] and is

dependent on the severity of CKD [3]. Traditional vascular risk factors, such as diabetes mellitus (DM), hypertension and dyslipidemia, are associated with a 20–40 % increased risk of clinical dementia [4]. Hypertension by itself may lead to brain white matter disease, lacunar infracts and cerebral micro- and macrobleeds, findings that associated with cognitive impairment. On the other hand in CKD patients, cognitive impairment may occur due to the presence of other metabolic risk factors, that is, uremia, inflammation, oxidative stress or anemia.

Our purpose of this study was to investigate the contribution of CKD to cognitive dysfunction in addition to hypertension among hypertensive patients with CKD and to evaluate the factors associated with the presence of CO/DY in all CKD stages and in patients on hemodialysis (HD) and peritoneal dialysis (PD), in comparison with hypertensive subjects without CKD.

Methods

Study population

In this study we included the following three groups of patients: (a) hypertensive subjects with a history of hypertension at least in the past 2 years, receiving antihypertensive agents; (b) patients in CKD stages I–IV according to Kidney Disease Outcomes Quality Initiative (KDOQI) classification stages I–IV [5], undergoing regular follow-up; and (c) patients on dialysis (HD and PD) for at least 3 months. The HD patients received 4 h of hemodialysis, three times a week, using bicarbonate dialysate. The PD patients were on a standard continuous ambulatory PD schedule using 1.5 or 2.5 % glucose dialysate. Exclusion criteria were as follows: (a) diagnosis of depression or delirium according to the history and neuropsychological tests, (b) history of prior stroke or transient ischemic attack documented in the medical chart and (c) low hemoglobin (Hb) level <10 g/dl.

Data accumulation

We collected the demographic data of the patients including age, height, weight, blood pressure measurements, duration of dialysis and educational status. Educational level was categorized as lower versus higher education; the former refers to secondary while the latter to tertiary education. Furthermore, other cardiovascular (CV) risk factors and CV disease (CVD), such as history of hypertension, history of DM, history of myocardial infarction, dyslipidemia and smoking status, were recorded. Smoking status was defined as current or past smoker versus non-smoker. Body mass index (BMI) was also calculated. The average of three blood pressure measurements with at least 2-min interval between them was recorded as the patient's representative blood pressure level. The difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP) was defined as pulse pressure (PP). Laboratory values for all groups were obtained within 30 days before cognitive testing. Dialysis dose, or equilibrated Kt/V, is a measurement used to assess the adequacy of dialysis treatment. KDOQI guidelines define an adequate dialysis, measured by an equilibrated (double poll) Kt/V as >1.00 for HD patients and >1.6 for PD patients [5]. The study protocol was conducted between July 2008 and November 2011 and was approved by the local ethical committee. Patients who participated in the study were informed and granted a formal consent.

Cognitive function assessment

Cognitive function was estimated by using six questionnaires, standardized for the general population of the country. For the assessment of executive and visual function, we used the clock-drawing test [6]; clock-drawing test has been extolled as an inexpensive, fast, qualitative tool for identifying dementia in clinical practice. The scale assigns up to 7 points based on three categories: time (3 points), numbers (2 points) and spacing (2 points) with a score of seven being perfect.

For the global cognitive function we used the Mini Mental State Examination (MMSE) [7]; it is a widely used test for global function. MMSE is a brief-point cognitive measure assessing the following domains: orientation, memory, attention, concentration, language and praxis. A full score on the MMSE is 30; higher scores indicate higher function where cognitive impairment was defined as a score of ≤ 26 and cognitive dysfunction as a score of ≤ 19 (Supplementary Table 1). For the executive function we used the instrumental activity of daily living (IADL) [8] test.

To assess the patients' psychological status, we used the Geriatric Depression Scale (GDS) [9], the Abbreviated Mental Test Score (AMTS) [10] and the Neuropsychiatric Inventory-Clinical rating scale (NPI-C) [11]. However, patients positive even in one of the psychological tests were excluded from the study. Questionnaires were administered by the same neurologist (H-SP). Patients were tested during a morning visit in a silenced room. Neuropsychological tests were conducted on HD patients before the dialysis session in the middle of the week, while on PD patients those were performed during their regular monthly visit.

Outcomes

We considered as outcome cognitive impairment measured by three separate tools, that is, MMSE, clock test and IADL. Based on the literature, each of these tests divides the population into individuals with normal cognitive function, mild, moderate and severe cognitive impairment according to the score for the diagnosis of CO/DY [6–13]. These tests assess three cognitive domains (memory, executive function and language) and classify a subject according to the cognitive function. The frequency of cognitive impairment in each group was described by the MMSE, since this examination has been proved to be a reliable test for screening patients for their global cognitive function [14].

Laboratory investigations

Blood samples were analyzed in an on-site biochemistry laboratory using standard automatic clinical chemistry techniques and an Olympus A U 600 (Olympus diagnostic Hamburg) analyzer. Blood chemistries, including creatinine measurement, was done with the Jaffe method. Serum parathormone (PTH) was measured with the Nichols Institute-immunoradiometric assay (N-IRMA), and C-reactive protein (CRP) was measured immediately after blood sampling by immunoturbidimetry (biochemistry analyses Integra 800, Roche). Twenty-four-hour urine collection was performed in hypertensives and the CKD I–IV patients. Urine total protein excretion was measured with an Olympus AU 600 (Olympus diagnostic Hamburg).

Statistical analysis

Data were presented as absolute numbers for binary variables and as mean with standard deviation (SD) for continuous variables. Comparisons between patient groups were performed using chi-square or Fisher's exact test for binary variables, and one-way analysis of variance (ANOVA) for continuous variables.

To investigate whether there was any potential relation between CO/DY and patient characteristics, for each group of patients, we compared whether patients with moderate or severe cognitive impairment, as it was defined by each of the three outcomes, that is, clock-drawing test, MMSE and IADL, differed significantly from patients with normal cognitive function or mild impairment. For this reason, we created three dummy variables, each for every outcome (clock-drawing test, MMSE and IADL), that included two categories each: one for patients with normal function or mild cognitive impairment and another for patients with moderate or severe cognitive impairment.

For analysis purposes, we used categorical variable "stages" to describe whether a patient was hypertensive without CKD, had CKD I–IV or were included in the dialysis group. Specifically, "stages" included five categories: hypertensive without CKD, CKD I–II, CKD III, CKD IV and patient on dialysis. We evaluated CKD stages I and II together since the number of patients in each group was rather small and in both groups uremic syndrome practically does not exist. We also transformed PP to a binary variable including patients with PP >60 mmHg and patients with PP ≤ 60 mmHg as categories. In addition, dialysis patients were categorized as patients with Kt/V >1.2 and patients with Kt/V ≤ 1.2.

For each group, first we performed univariate logistic regression analysis for each variable. All variables with a p value of <0.1 in the univariate analysis were further evaluated in a backward stepwise multivariate regression analysis. Odds ratio (OR) with the corresponding confidence interval (CI) was calculated for each variable in the multivariate model, and a two-sided p value <0.05 was considered as statistically significant. Statistical analyses were performed using the statistical package SPSS, version 16.0 (SPSS Inc). All p values <0.05 were considered statistically significant.

Results

Two hundred fifty-six subjects were finally enrolled: 96 hypertensives, 19 patients with CKD stages I–III, 33 patients with CKD III, 42 patients with CKD stage IV, 33 patients treated with HD and 33 patients on PD. According to MMSE scores, patients with CKD stages I–II had 5.1 % mild, 4.7 % moderate and 1.9 % severe CO/DY. Patients with CKD stages III had 10.2 % mild, 29.5 % moderate and 3.8 % severe CO/DY. In patients with CKD stage IV, 26.2 % had mild, 14.2 % moderate and 19 % severe CO/DY. Among hypertensive patients 71.5 % had normal cognitive function, 26.5 % mild and 2 % moderate CO/DY. None of the hypertensive subjects had severe CO/DY. Of the 66 patients on dialysis, 31.9 % had normal, 24.2 % mild, 16.6 % moderate and 27.3 % severe CO/DY. Severe CO/DY was evident in 45.4 % of HD versus 9 % of PD patients.

Baseline demographic and biochemical data are summarized in Tables 1 and 2, respectively.

CKD I–II patients were younger and had less often CVD and DM than the other groups of the study (Table 1). There were no significant differences between HD and PD patients regarding age, sex distribution, blood pressure levels, educational level and dialysis vintage (Table 1). Frequency of DM and history of CVD were significantly different between HD and PD (48 % vs. 9.1, $p = 0.01$) patients (Table 1). HD patients had significantly higher mean serum PTH levels (322 ± 171.8) compared to PD patients (191.4 ± 107.2, $p < 0.005$; Table 2). In hypertensive subjects TGR, albuminuria and CRP levels were significantly lower as compared to CKD patients, while HDL-C and serum albumin were significantly higher. Hypertensive patients had also less proteinuria and significantly better GFR-MDRD (ml/min/1.7 m^2) than CKD patients (Table 2).

Main analyses of the total CKD population

MMSE

In univariate analysis, CKD stages (OR 2.33, 95 % CI 1.84–2.96; $p < 0.001$), age (OR 1.09, 95 % CI 1.05–1.13; $p < 0.001$), DM (OR 5.55, 95 % CI 2.58–11.89; $p < 0.001$), PTH (OR 1.01, 95 % CI 1.00–1.00; $p < 0.001$) and DBP (OR 0.97, 95 % CI 0.93–0.99; $p = 0.02$) were associated with CO/DY (Supplementary Table 2). In multivariate analysis, CKD stages (OR 2.46, 95 %C CI 1.81–3.34; $p = 0.001$), age (OR 1.06, 95 %CI 1.02–1.09; $p = 0.001$), DM (OR 4.27, 95 %CI 1.88–9.75; $p = 0.001$) and PTH levels (OR 1.01, 95 %CI 1.00–1.01; $p = 0.010$) remained as independent predictors of CO/DY (Table 3).

Clock-drawing test

In univariate analysis, CKD stages (OR 2.46, 95 % CI 1.81–3.34; $p < 0.001$), age (OR 1.08, 95 % CI 1.04–1.14; $p < 0.001$), DM (OR 6.13, 95 % CI 2.78–13.44; $p < 0.001$), PTH levels (OR 1.05, 95 % CI 1.02–1.08; $p = 0.006$) and DBP (OR 0.96, 95 % CI 0.94–0.92; $p = 0.01$) were associated with CO/DY (Supplementary Table 2). In multivariate analysis, CKD stages (OR 1.92, 95 % CI 1.23–2.99; $p = 0.004$), age (OR 1.07, 95 % CI 1.03–1.11; $p = 0.001$), DM (OR 4.48, 95 % CI 1.86–10.83; $p = 0.001$) and PTH levels (OR 1.92, 95 % CI 1.23–2.99; $p = 0.004$) were associated with CO/DY (Table 3).

IADL

In univariate analysis, CKD stages (OR 1.9, 95 % CI 1.47–2.48; $p < 0.001$), age (OR 1.2, 95 % CI 1.07–1.17; $p < 0.001$), DM (OR 9.54, 95 % CI 4.34–20.97; $p = 0.001$), UTPR (OR 1.00, 95 % CI 1.00–1.00; $p = 0.02$), levels of serum Ca^{++} (OR 0.44, 95 %CI 0.23–0.83; $p = 0.01$) and $Ca^{++}xPO_4^{-}$ (OR 0.62, 95 % CI 0.93–0.97; $p = 0.02$) were associated with CO/DY (Supplementary Table 2). In multivariate analysis, CKD stages (OR 1.75, 95 % CI 1.26–2.45; $p = 0.001$), age (OR 1.11, 95 % CI 1.05–1.16); $p < 0.001$), DM (OR 7.64, 95 % CI 3.12–18.73); $p < 0.001$) and UTPR levels (OR 1.00, 95 % CI 1.00–1.00); $p = 0.04$) were associated with CO/DY (Table 3).

Hypertensive patients without CKD

MMSE

In univariate analysis, age (OR 0.08, 95 % CI 0.02–0.0.15; $p = 0.01$), DM (OR 0.41, 95 % CI 0.03–0.80; $p = 0.03$) and PP >60 mmHg (OR 0.204, 95 % CI 0.001–0.406; $p = 0.004$) were associated

Table 1 Baseline characteristics of the study population

	Hypertensives ($n = 96$)	CKD I-II ($n = 19$)	CKD III ($n = 33$)	CKD IV ($n = 42$)	HD ($n = 33$)	PD ($n = 33$)	p_1 value	p_2 value
Age (years), mean ± SD	53 ± 1.51	50.2 ± 11.8	63.1 ± 9.4	64.1 ± 12.2	60.4 ± 13.8	58.6 ± 15.7	0.05	NS
Sex (male/female), *n* (%)	62/35 (63.9/36.1)	15/4 (78/22)	20/9 (60/27)	33/14 (70.2/29.8)	17/14 (54.8/45.2)	20/13 (60.6/39.4)	0.05	NS
BMI (kg/m^2), mean ± SD	30.7 ± 2.1	32.2 ± 12.8	27.2 ± 6.4	26.8 ± 5.1	25.1 ± 3.2	25.8 ± 3.5	NS	NS
SBP (mmHg)	138.2 ± 14.6	134 ± 10.4	140 ± 11.2	144 ± 22.2	132 ± 21	132 ± 20	NS	NS
DBP (mmHg)	83.1 ± 10.1	80.3 ± 10.6	78.2 ± 11.8	78 ± 11.6	77.4 ± 10.6	78.7 ± 11.5	NS	NS
PP (mmHg)	57.6 ± 16.8	61 ± 28.8	78.2 ± 11.8	72.1 ± 11.7	51.1 ± 20.9	50.4 ± 16.5	NS	NS
Higher education level[a], *n* (%)	53 (55)	14 (73)	18 (54)	8 (19)	3 (9)	5 (15)	0.01	NS
Hx DM, *n* (%)	7 (7.2)	4 (21)	8 (24.4)	16 (38)	16 (48.8)	3 (9.1)	0.02	0.01
Hx CVD[b], *n* (%)	1 (1)	1 (0.05)	3 (9)	6 (14.2)	8 (24.2)	5 (15.2)	0.01	0.05
Hx hypertension, *n* (%)	96 (100)	16 (84)	28 (85)	42 (95)	29 (87)	28 (85)	0.01	NS
Smokers, *n* (%)	4 (4.1)	2 (10)	7 (21.2)	6 (12.1)	4 (12.1)	3 (9.1)	NS	NS
Duration of dialysis (months), mean ± SD	NA	NA	NA	NA	31.6 ± 13.6	23.9 ± 22.1	NS	NS
Kt/V	NA	NA	NA	NA	1.27 ± 0.23	2.27 ± 0.8	NA	NS
Medications, *n* (%)								
ACEis/ARBs	60 (62.5)	16 (84)	27 (81)	29 (69.4)	11 (33.3)	14 (42.2)	0.01	NA
CCBs	32 (33.3)	12 (63)	13 (39)	33 (78.5)	12 (36.3)	15 (45.4)	0.01	NA
Monotherapy CCBs[c]	27 (28.2)	4 (73)	6 (18)	4 (9.5)	0	0	0.05	NA
Monotherapy RAAS	56 (58.3)	6 (31)	12 (36)	2 (4.7)	0	0	0.05	NA
Erythropoietin	0	2 (10)	7 (21)	27 (60.2)	17 (40.4)	26 (78.8)	0.01	NA
Statins[d]	1 (1)	4 (21)	16 (48)	19 (45.2)	14 (33.1)	21 (63.6)	0.01	NA
Vitamin D analogs[e]	12 (12.5)	2 (10)	21 (63)	21 (50)	28 (84)	22 (66)	0.01	NA

SD standard deviation, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *PP* pulse pressure, *Hx DM* history of diabetes mellitus, *Hx CVD* history of cardiovascular disease, *Hx hypertension* history of hypertension, *Kt/V* marker of dialysis adequacy, *NA* non-applicable, *ACEis* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor antagonist, *CCBs* calcium channel blockers, *RAAS* renin–angiotensin–aldosterone system

p_1 value represents ANOVA for all groups, while p_2 value represents *t* test analysis between HD and PD patients

[a] Education level: lower versus higher education

[b] Hx CVD: history of cardiovascular disease including positive angiography and/or acute coronary episode and/or coronary artery bypass surgery

[c] Monotherapy CCBs/RAAS: patients received as monotherapy one agent of antihypertensive treatment

[d] Statin analog included Atorvastatin or Rosuvastatin

[e] Vitamin D analogs included alfa-calciferol or paricalcitol

with CO/DY (Supplementary Table 3). In multivariate analysis, age (OR 0.006, 95 % CI 0.001–0.013; $p = 0.05$) was associated with CO/DY (Table 4).

Clock-drawing test

In univariate analysis, age (OR 0.05, 95 % CI 0.01–0.09; $p = 0.002$), DM (OR 0.48, 95 % CI 0.24–0.72; $p = 0.001$) and PP >60 mmHg (OR 0.20, 95 % CI 0.07–0.33; $p = 0.003$) were associated with CO/DY (Supplementary Table 3). In multivariate analysis, PP >60 mmHg (OR 0.17, 95 % CI 0.04–0.29; $p = 0.007$) was associated with CO/DY (Table 4).

IADL

In univariate analysis, DM (OR 0.49, 95 % CI 0.15–0.82; $p = 0.001$) and PP >60 mmHg (OR 0.26,

Table 2 Baseline biochemical characteristics of the study population

	Hypertensives ($n = 96$)	CKD I-II ($n = 19$)	CKD III ($n = 33$)	CKD IV ($n = 42$)	HD ($n = 33$)	PD ($n = 33$)	p_1 value	p_2 value
Ht (%)	42.9 ± 3.7	40.9 ± 3.5	38.3 ± 4.1	37.5 ± 4	37.5 ± 4	37.7 ± 4.7	NS	NS
Hb (g/dl)	13.7 ± 1.5	13.5 ± 1.3	12.6 ± 1.4	11.4 ± 1.2	11.4 ± 1.2	12.1 ± 1.7	0.04	NS
T-CHOL (mg/dl)	205 ± 39.4	209 ± 48.8	202 ± 44.7	166 ± 33	168 ± 33	190 ± 42	NS	NS
TRG (mg/dL)	127 ± 47.5	141 ± 72.4	145 ± 64.5	174 ± 79	165 ± 78	153 ± 76	0.05	NS
HDL-C (mg/dL)	52 ± 131	56 ± 14.8	52.7 ± 16.5	42.0 ± 10.3	56 ± 10.5	48.6 ± 13.3	0.02	NS
Ca^{++} (mg/dL)	9.7 ± 0.4	9.8 ± 0.4	9.7 ± 0.7	9.4 ± 0.5	9.3 ± 0.5	9.5 ± 0.6	NS	NS
PO_4^- (mg/dL)	3.42 ± 0.4	3.4 ± 0.5	3.4 ± 0.8	5.3 ± 1.2	5.3 ± 1.2	5.1 ± 1.3	0.001	NS
$Ca^{++}xPO_4^-$	33.4 ± 4.8	39.7 ± 9.3	33.4 ± 7.3	49.4 ± 11.9	49.1 ± 12.1	48.6 ± 13.2	0.001	NS
PTH (pg/ml)	40.2 ± 13.2	49.1 ± 36.2	82.3 ± 69.2	322.9 ± 171.8	306 ± 192	191.4 ± 107.2	0.001	0.005
sAlb (gr/dl)	4.5 ± 0.29	4.1 ± 0.5	3.8 ± 0.4	4.1 ± 0.6	3.8 ± 0.36	3.7 ± 0.5	0.05	NS
CRP (mg/l)	1.9 ± 0.6	3.5 ± 2.2	3.9 ± 3	3.5 ± 2.7	7.4 ± 10.8	4.4 ± 4.8	0.001	NS
UTPR (mg/dl)[a]	188 ± 92	1,650 ± 230	1,180 ± 1,460	1,300 ± 225	NA	NA	0.001	NA
GFR-MDRD (ml/min/ 1.7 m^2)	88 ± 2.1	74 ± 14	44.8 ± 10	17.5 ± 6.9	NA	NA	0.001	NA

Values correspond to mean ± SD

Ht hematocrit, *Hb* hemoglobin, *T-chol* total cholesterol, *TRG* triglycerides, *HDL-Chol* high-density lipoprotein cholesterol, Ca^{++} calcium, PO_4^- phosphorus, $CaxPO_4$ product of calcium x phosphorus, *PTH* parathormone, *sAlb* serum albumin, *CRP* C-reactive protein, *UTPR* urine total protein excretion, *MDRD* modification of diet in renal disease

[a] In hypertensive subjects proteinuria levels were on microalbuminuria levels (30–300 mg/g (0.03 and 0.3 g/g)

Table 3 Multivariate analysis of non-dialysis population

Cognitive tests	Factor	OR (95 % CI)	p
MMSE	Stages	2.46 (1.81–3.34)	<0.001
	Age (years)	1.06 (1.02–1.09)	0.001
	DM	4.27 (1.88–9.75)	0.001
	PTH	1.01 (1.00–1.01)	0.010
Clock test	Stages	1.92 (1.23–2.99)	0.004
	Age (years)	1.07 (1.03–1.11)	0.001
	DM	4.48 (1.86–10.83)	0.001
	PTH	1.92 (1.23–2.99)	0.004
IADL	Stages	1.75 (1.26–2.45)	0.001
	Age (years)	1.11 (1.05–1.16)	0.000
	DM	7.64 (3.12–18.73)	0.000
	UTPR	1.00 (1.00–1.00)	0.047

For MMSE and clock-drawing test, higher score is better, while for IADL high score is worse. Variation of scale: MMSE (0–30), clock-drawing test (0–7), IADL (9–27)

MMSE Mini Mental State Examination, *Clock test* clock-drawing test: executive function, visual–spatial, *IADL* instrumental activities of daily living: executive function, *DM* diabetes mellitus, *PTH* parathormone, *UTPR* urine total protein excretion, *DD* duration of dialysis

Cognitive impairment algorithm; 6–13

Table 4 Multivariate analysis of subgroup (non-CKD hypertensive patients)

Cognitive tests	Factor	OR (95 % CI)	p
MMSE	Age (years)	0.006 (0.001–0.013)	0.005
Clock test	PP ≤60 mmHg	0.17 (0.04–0.29)	0.007
IADL	Age (years)	0.012 (0.006–0.017)	0.001
	PP ≤60 mmHg	0.162 (0.001–0.324)	0.005
	Mono CCBs	0.16 (0.01–0.34)	0.034

95 % CI 0.09–0.44; $p = 0.003$) were associated with CO/DY (Supplementary Table 2). In multivariate analysis, age (OR 0.012, 95 % CI 0.006–0.017; $p = 0.001$), PP >60 mmHg (OR 0.162, 95 % CI 0.001–0.324; $p = 0.05$) and CCB as monotherapy (OR 0.16, 95 % CI 0.01–0.34; $p < 0.03$) were associated with CO/DY (Table 4). On the other hand, 56 (58.3 %) hypertensive subjects receiving renin–angiotensin–aldosterone system (RAAS) blockade agents as monotherapy did not reveal better executive function, compared to patients not receiving RAAS blockade agents (OR 1.02, 95 % CI 0.96–1.09; $p < 0.338$).

Dialysis patients

MMSE

In univariate analysis, in the subgroup of hemodialysis patients (HD vs. PD), dialysis modality (OR 0.22, 95 % CI 0.74–0.66; $p = 0.007$), DM (OR 11.2, 95 % CI 1.28–98.43; $p = 0.02$) and Hb <11 g/dl (OR 0.18, 95 % CI 0.04–0.78; $p = 0.021$) were associated with CO/DY (Supplementary Table 4). In multivariate analysis, DM (OR 13.2, 95 % CI 1.22–142.64; $p = 0.001$) and Hb <11 g/dl (OR 0.14, 95 % CI 0.02–0.82; $p = 0.001$) were associated with CO/DY (Table 5).

Clock-drawing test

In univariate analysis, modality (OR 0.12, 95 % CI 0.04–0.38; $p < 0.001$), age (OR 1.12, 95 % CI 1.05–1.21; $p = 0.001$) and levels of PO_4^- (OR 0.53, 95 % CI 0.29–0.96; $p = 0.03$) were associated with CO/DY. In multivariate analysis, PD patients were less likely to present with CO/DY (OR 0.12, 95 % CI 0.03–0.51; $p = 0.003$) (Supplementary Table 4). In addition, age (OR 1.12, 95 % CI 1.05–1.21; $p = 0.001$) was independently associated with CO/DY.

IADL

In univariate analysis, age (OR 1.08, 95 % CI 1.02–1.15; $p = 0.01$), $Ca^{++}xPO_4^-$ (OR 0.93, 95 % CI 0.88–0.99; $p = 0.03$) and Kt/V >1.2 (OR 0.05, 95 % CI 0.07–0.56; $p = 0.01$) were associated with CO/DY (Supplementary Table 4). In multivariate analysis, age (OR 1.12, 95 % CI 1.01–1.22; $p = 0.01$) and Kt/V >1.2 (OR 0.05, 95 % CI 0.004–0.68; $p = 0.024$) were associated with CO/DY (Table 5).

Table 5 Multivariate analysis of subgroup (dialysis patients)

Cognitive tests	Factor	OR (95 % CI)	*p*
MMSE	DM	13.21 (1.22142.64)	0.001
	Hb <11 g/dl	0.14 (0.02–0.82)	0.001
Clock test	Modality (HD/PD)	0.12 (0.03–0.51)	0.003
	Age (years)	1.12 (1.05–1.21)	0.001
	Age (years)	1.12 (1.01–1.22)	0.018
IADL	Kt/V >1.2	0.05 (0.004–0.68)	0.024

Discussion

The main finding of the study was that in every CKD stage the risk of CO/DY increased more than twofold. Our results are in accordance with the previous studies, and CO/DY is evident even at the early stages of CKD. The Heart, Estrogen/Progesterone study showed that in a menopausal woman, each 10 ml/min/1.73 m^2 decrement in eGFR corresponded to an approximately 15–25 % increase in the risk of CO/DY [15]. A recent meta-analysis assessing the impact of CKD on cognitive decline suggested that CKD is a significant and independent somatic risk factor in the development of cognitive decline [16]. In our CKD patients, low Hb levels (Hb <11 g/dl) and increased serum PTH levels are associated with increased CO/DY. It seems that a number of modifiable factors may affect the patient's cognitive function during the progression of CKD. In patients with CKD, systematic microvascular disease caused by diabetes, hypertension, anemia and elevated inflammatory factors involving both renal and cerebral vasculature are the potential mechanisms that account for cognitive impairment [17–20].

In all groups of our study, DM patients revealed a worst CO/DY. The finding in CKD I–IV and HD patients remains significant also in multivariate analysis. Our results are in accordance with the recent studies and suggest an additive contribution of DM to CO/DY [21, 22].

In hypertensive subjects PP ≤60 mmHg and the use of CCBs may have a positive impact on CO/DY. The association between increased blood pressure and cognitive functioning is still under debate. Hypertension is considered to be a risk factor for vascular dementia and Alzheimer's disease [23], and poor blood pressure control is associated with an even greater cognitive decline [24]. Theoretically, high blood pressure levels could either prevent or enhance cognitive impairment. Recent evidence focusing on the elderly population showed that decline in SBP is associated with better verbal fluency and memory. Both an increase and a decline in SBP are associated with better MMSE test scores. Changes in DBP are not related to cognitive functioning [25]. In our

hypertensive subjects, age and PP >60 mmHg were associated with severe CO/DY. The ongoing SBP Intervention Trial (SPRINT) will assess, in a multicenter randomized design, whether maintaining blood pressure levels lower than current recommendations further reduces the risk of age-related cognitive decline in patients with and without CKD [26].

As we mentioned above in our group of hypertensives receiving monotherapy with CCBs, a better executive cognitive function was evident. A recent study [27] demonstrated the important effect of CCBs on cognitive decline, independently of the blood pressure level and the existence of macro- or microvascular alterations, suggesting a specific neuroprotective effect of this pharmacological drug class. Interventional controlled trials are required to confirm the specific protective effect of CCBs on cognitive decline.

Surprisingly, in our study monotherapy with a RAAS blocker had no effect on CO/DY (data not shown). This finding is not in agreement with recent information demonstrating that therapy with an ACE inhibitor may prevent the major subtype of vascular dementia known as post-stroke cognitive decline [28]. Three randomized studies evaluated dementia as an outcome, in a secondary prevention, in elderly hypertensive patients. In Syst-Eur and Progress studies, active treatment was associated with 50 and 19 % reduction in dementia incidence, respectively, in participants with the history of stroke [29]. However, the Study on Cognition and Prognosis in the Elderly (SCOPE) compared candesartan with placebo in 70–89 aged patients with hypertension, over 44 months, and found no differences in cognitive outcomes between the 2 groups [30]. Post hoc analysis of the study reported a less cognitive decline among patients with mild cognitive impairment at baseline, in the candesartan-treated group ($p < 0.04$). These results are not in agreement with our study.

Our HD patients had a worst CO/DY compared to PD patients. Cognitive impairment in HD patients could also be due to the dialysis process, which results in large acute intravascular volume loss and fluid shifts, leading to cerebral edema, decreased cerebral perfusion and cerebral ischemia. The process may cause silent cerebrovascular disease, which may contribute to cognitive impairment [31, 32]. On the other hand, in PD patients, a variety of biochemical abnormalities have been invoked to explain the cognitive defects such as the uremic syndrome, including decreased cellular energy utilization, abnormalities in both extracellular and intracellular electrolyte concentrations, toxic accumulations of a variety of compounds in combination with the effect of sodium retention and the increased intracranial pressure [33]. In a recent study [34], including 57 PD patients without diabetes, it was found that PD procedure itself seems to be associated with the presence of leukoaraiosis and cognitive impairment. Therefore, maintaining stable cognitive function using gentler dialysis treatment options may be very important to our patients.

In dialysis patients, low Hb levels (Hb <11 g/dl) were associated with severe CO/DY. Our observation confirms previous evidence that anemia was a risk factor for cognitive impairment in dialysis patients [35, 36].

An interesting finding was that serum PTH levels were associated with severe CO/DY, in particular with the global cognitive function and the executive function.

In the total population in univariate analysis, we did find a significant association between the serum Ca^{++} levels, the $Ca^{++}xPO_4^-$ product and the CO/DY; however, this association was not significant in the multivariate analysis. Phosphate binders may reduce the $Ca^{++}xPO_4^-$ product. Information regarding this effect in CO/DY is limited. In a study using lanthanum carbonate as a phosphate binder, it was found that lanthanum did not adversely affect cognitive function compared with the standard therapy in HD patients over a 2-year time period [37].

In HD patients the quality of dialysis expressed with equilibrated Kt/V >1.2 was also a factor with a significant association with severe CO/DY. Our results confirm the data of Muray et al. [38], who found that equilibrated Kt/V >1.2 was associated with severe cognitive impairment in 338 HD patients.

Limitations in our study were the relatively small number of patients in each group and the hierarchy of the design which is cross sectional and is always subject to residual confounding which cannot be excluded. However, we think that the inclusion of patients from all CKD stages and both renal replacement modalities, together with hypertensive patients used as controls, permit the cross-sectional design. In addition, one can argue that the tests we used (MMSE

and AMTS) are primarily used to screen for dementia. However, there is also mild cognitive impairment, which does not meet the criteria for dementia. A test that detects also mild cognitive impairment, which we do not use in our study, is the Trail Making Test B [39]. This test compared to the modified MMSE showed a much greater decline of cognitive function over the stages of CKD [40].

In conclusion, in every CKD stage progression, the risk of CO/DY increased significantly. A number of different modifiable and non-modifiable factors may affect the hypertensive and CKD patient's cognitive function. In CKD patients, CKD stage progression, low Hb levels (Hb <11 g/dl) and increased serum PTH levels are associated with increased CO/DY while DM plays also a significant role in cognitive function deterioration. Among hypertensive patients, those with PP ≤60 mmHg or receiving CCBs may have a better executive function. Much remains to be learned regarding the modifiable factors and its effect on cognitive function.

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