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"Does chronic kidney disease define a particular risk pattern of cerebral vessels modifications in patients with symptomatic ischemic cerebrovascular disease?"

Research Article

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Abstract: Cardiovascular complications, including stroke, may be attributed the highest rate of morbidity and mortality in patients with chronic kidney disease (CKD). The aim of our study was to evaluate the prevalence of CKD in patients with symptomatic ischaemic cerebrovascular disease and to establish of whether CKD may define a particular risk pattern of cerebral vessels modifications in this category of patients. The prevalence of CKD was evaluated in 590 consecutive patients with symptomatic ischaemic cerebrovascular disease admitted to a department of neurology. The types of stroke, the vascular territories, the vascular modifications and the haemodynamic changes (resistance index- RI) found by neurosonology (extracranial and transcranial Doppler ultrasound) were analysed in relation to classic and non-classic cerebrovascular risk factors, as well as to stages of CKD (defined by estimated glomerular filtration rate-eGFR-MDRD4 formula-K/DOQI 2002). The prevalence of CKD in the studied patients was 70.84%. Atherosclerosis in a diffuse pattern was detected in 79.7% of CKD patients, while carotid artery stenoses were found in 10% of cases, occlusions- 5.3%, stenoses + occlusions- 1.2%, and multiple stenoses- 3.8% of cases. The RI evaluated in the internal carotid arteries correlated with fibrinogen($P<0.0001$) and GFR($P<0.0001$), while IR in the middle cerebral arteries correlated with fibrinogen($P<0.05$), C-reactive protein($P<0.0001$), and GFR($P<0.0001$). There is a strong relation between symptomatic cerebrovascular disease and CKD, a fact demonstrated by the increased prevalence of CKD in these patients and by the severity of the cerebral vessels lesions.

Keywords: *Cerebrovascular disease • Chronic kidney disease • Extracranial Doppler ultrasound • Risk factors • Transcranial Doppler ultrasound*

1. Introduction

Cardiovascular complications, including stroke, may be attributed the highest rate of morbidity and mortality in patients with chronic kidney disease (CKD) and may reflect the involvement of the vascular system in relation to its deriving metabolic consequences.

In a representative sample of 7,690 middle-aged British men who were monitored, for clinical purposes, for 15 years, the risk of stroke was 60% higher for the subgroup with a serum creatinine level greater than 1.3 mg% than for those with lower values, even after

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adjustment for several other cardiovascular risk factors [1].

The predictive value of mild renal insufficiency for the occurrence of cardiovascular complications in the general population has been documented in a study carried out in a randomized cohort of subjects, age 45-64 years - Atherosclerosis Risk in Communities (ARIC) Study. The results of this study provided evidence that minor renal function impairment was recorded in 50% of cases, and of these, 5% had coronary heart disease, while 4.8% presented with symptoms or history of cerebrovascular disease [2].

Moreover, in the Cardiovascular Heart Study which enrolled subjects over the age of 65 years who were followed up for 7 years, 11% of the subjects presented with impaired renal function. The prevalence of overt clinical forms of cardiovascular disease (coronary heart disease, cerebrovascular disease), as well as of asymptomatic forms of cardiovascular disease (assessed through echocardiography, carotid ultrasound) was 64% by comparison with a prevalence of 43% of the parameters studied in subjects with normal renal function [3]. Furthermore, data provided by the KEEP and NHANES studies show that CKD was independently associated with myocardial infarction or stroke in participants in a voluntary health-screening program and a randomly selected population [4].

The aim of our study was to evaluate the prevalence of CKD in patients with symptomatic ischemic cerebrovascular disease and to establish of whether CKD may define a particular risk pattern for pathological modifications of the cerebral vessels in this category of patients. Also, we analysed the predictive value of the neurosonological methods (extracranial Doppler-ECD and transcranial Doppler-TCD) in the stratification of the severity of the cerebral vessels lesions in patients with symptomatic ischemic cerebrovascular disease and CKD and in the detection of a potential association with similar vascular changes in other vascular beds.

2. Material and Methods

2.1. Study design

The study was conducted on 590 consecutive symptomatic patients with ischemic cerebrovascular disease out of 1190 patients admitted to the 2nd Dpt. of Neurology, County Emergency Hospital Timisoara from January 2003 through December 2007. In the study were included only patients whose charts provided consistent data, suitable for the purposes of the study. Patients whose charts failed to provide accurate data were excluded. Also, patients with cardioembolic stroke were excluded from the study. None of the patients was on renal replacement therapy, nor did they undergo renal transplantation.

All patients enrolled were evaluated with regard to the types of stroke, the corresponding vascular territories and the vascular modifications consistent with cerebral vessels atherosclerotic and arteriosclerotic found by ECD and TCD.

The prevalence of the cerebral vessels modifications found by ultrasound was assessed in relation to the stages of CKD and correlation analyses were performed between the neurosonological findings, and classic and non-classic cerebrovascular risk factors within the frames of CKD.

The neurological diagnosis and the types of ischemic cerebrovascular disease (infarction or transient ischemic attack - TIA), as well as of cardiovascular co-morbidities were established according to the *International Classification of Disease*, 9th and 10th Revision (ICD-9, ICD-10) codes. In order to establish the topographic diagnosis of cerebrovascular disease, all patients underwent cerebral computed tomography (CT scan) and/or cerebral MRI. Localized cerebral vessels lesions (stenosis and occlusions) were also assessed through cerebral MRI-angiography. In addition, in cases with severe carotid artery stenosis and occlusions referred to interventional therapies, 4-vessel conventional cerebral angiography was performed.

CKD was defined as either kidney damage (pathological abnormalities or markers of damage including abnormalities in blood or urine samples) or GFR< 60ml/min for over 3 months. The stages(1-5) of CKD were established according to the K/DOQI Guidelines 2002, revised by the KDIGO Guidelines 2005 (estimated GFR-MDRD4 equation formula stage1 GFR>90 ml/min/1.73m^2; stage2 GFR-60-90 ml/min/1.73m^2; stage3 GFR-30-60 ml/min/1.73m^2; stage4 GFR-30-15 ml/min/1.73m^2; stage5 GFR<15 ml/min/1.73m^2 [5].

Coronary heart disease (CHD) was assessed by clinical picture (stable angina, no previous interventional methods) and electrocardiography, whereas peripheral vascular disease (PVD) was evaluated by clinical data and peripheral Doppler ultrasonography. Diabetes was defined as a fasting glycaemia≥126mg/dl or use of insulin or hypoglycaemic medication. All patients were treated with antihypertensive medication (angiotensin converting enzyme inhibitors, calcium channel blockers, beta-blockers, diuretics). The study was approved by the Ethical Committee of the County Emergency Hospital Timisoara.

2.2. ECD and TCD ultrasound methods

All patients underwent cerebrovascular Doppler ultrasound examinations by means of a Doppler velocimeter with fast-Fourier spectral transformation analysis (Explorer CVC-Montpellier, France); a continuous- wave (4MHz-CW) probe was utilized for ECD exploration of the common carotid arteries, external carotid arteries, and the internal carotid arteries (ICA_s), bilaterally, with regard to their patency and the Pourcelot's resistance index (RI) in the ICA_s, which evaluates the distensibility and compliance of the sonorized arteries (systolic flow velocity (-) diastolic flow velocity / systolic flow velocity) (normal range RI<0.7) [6]; a pulsed-wave (2 MHz-PW) probe was utilised for TCD exploration of the middle cerebral arteries (MCA_s), bilaterally, through the transtemporal window at a depth of 50mm. The patency of the vessels and the RI were estimated for each MCA as described above. The ultrasound grading of carotid artery stenosis was established by measuring the modifications of spectral velocities and the levels of the peak systolic flow velocities (PSV) assessed by spectral transformation analysis, such as follows: Grade I (< 40% in surface; < 23% in diameter; PSV < 125 cm/sec); Grade II (40-60% in surface; 23-40% in diameter; PSV 125-230 cm/sec); Grade III (60-75% in surface; 40-50% in diameter; PSV > 230 cm/sec); Grade IV (75-90% in surface; 50-70% in diameter; PSV > 300 cm/sec); Grade V (> 90% in surface; > 70% in diameter; PSV >400 cm/sec, near occlusion)[6].

2.3. Statistical analysis

The clinical, biological and cerebrovascular Doppler data were expressed as means ± standard deviation (SD). Student's t-test was used to compare mean values at baseline among patients with and without CKD. Categorical data were compared with the use of Pearson chi-square test or Fisher exact test, as appropriate. Non-parametric variables were correlated using Spearman Rank Order test. Risk factors for cerebral vessels remodeling as assessed by cerebrovascular ultrasound were evaluated utilizing univariate logistic regression analysis. The independent variables that were statistically significant were entered into multivariate logistic regression models. Using backward elimination procedures, the most parsimonious multivariate logistic model was produced for predicting cerebrovascular modifications. Odds ratios (OR_s) and their 95% confidence intervals (CI) were calculated. Correlations between risk factors for cerebral vessels modifications and the RIs in the ICAs and MCAs were evaluated by multivariate regression analysis(Cox & Snell R square) in which only independent variables were introduced in the model. All *P* values were calculated based on two-sided statistical tests. Statistical significance was considered as $P<0.05$. Statistical analyses were performed using Epi Info v.3.2.2 and SPSS v.10 software.

3. Results

3.1. Characteristics of the subject groups

The prevalence of CKD in the studied patients was 70.84% (418 patients; males - 45.9%, females - 54.1%, mean age- 65.76±9.49 years). The comparison between characteristics of patients with and without CKD in terms of clinical, biological and cerebrovascular Doppler data is presented in Table 1. Hypertension was found in 86.8% of patients with CKD. CHD was recorded in 85.6% of cases with CKD, while PVD was detected in 39.5% of CKD (+) cases.

3.2. ECD and TCD ultrasound data

The prevalence of cerebral vessels modifications assessed by ECD and TCD ultrasound according to the CKD stage was as follows: stage 1- 38 patients (9%), stage 2 - 186 patients (45%), stage 3 - 165 patients (39%), stage 4 - 21 patients (5%), and stage 5 - 8 patients (2%).

Table 2 presents the types of cerebral vascular lesions assessed by ECD and TCD ultrasound in CKD (+) and CKD (-) patients. The topographic diagnosis of cerebrovascular disease in CKD(+) and CKD(-) patients, in relation to the vascular territories involved, assessed through CT scan and/or MRI, and correlated with the above-mentioned Doppler ultrasound modifications is presented in Table 3.

There was an 89% concordance between data found by Doppler ultrasound and the cerebral MRI-angiography in stenosis ($P<0.0001$) and of 100% ($P<0.0001$) in occlusions, respectively.

3.3. Risk factors for cerebral vessels

The CKD (+) group was divided in 2 subgroups: 305 patients with diffuse atherosclerosis of the carotid arteries and middle cerebral arteries (increased RIs) and 113 patients with more severe vascular lesions, namely stenosis (grades I to V) and occlusions in the carotid arteries. Cerebrovascular risk factors were assessed by univariate analysis in the two subgroups within the CKD (+) group and only the significant variables ($P< 0.25$) were included in the multiple logistic regression analysis. In the full model, cholesterol ($P<0.055$), fibrinogen ($P<0.001$), C-reactive protein ($P<0.001$),

Table 1. Clinical, biological and ultrasound data in CKD (+) and CKD (-) patients.

Parameter	Group CKD (+)n=418 Mean+/-SD	Group CKD(-)N=172 Mean+/-SD	t-test for Equality of Means P(2-tailed)
Age(years)	65.76+/-9.49	63.41 +/-9.81	0.007
SBP(mmHg)	158.49+/-22.91	126.86 +/-8.65	0.0001
DBP(mmHg)	88.94+/-12.38	73.87 +/-6.19	0.0001
Serum creatinine(mg/dl)	1.247+/-0.606	0.717 +/-0.013	0.0001
Glycaemia(mg/dl)	128.29+/-49.39	101.60 +/-15.15	0.0001
Cholesterol(mg/dl)	217.09+/-47.31	191.95+/-34.07	0.0001
Triglycerides(mg/dl)	162.94+/-80.56	137.06+/-62.02	0.0001
Fibrinogen(mg/dl)	430.73+/-68.35	260.28+/-40.10	0.0001
C-reactive protein(mg/dl)	2.6074+/-1.1794	0.6749+/-0.2984	0.0001
Proteinuria(g/24h)	1.07982+/-0.92021	0.13144+/-9.5022E-02	0.0001
GFR(ml/min/1.73m^2)	62.1887+/-19.7884	106.1233+/-10.6723	0.0001
RI-Right MCA	0.843+/-7.494E-0.2	0.700+/-0.031	0.0001
RI-Left MCA	0.843+/-7.497E-02	0.700+/-0.026	0.0001
RI-Right ICA	0.742+/-7.531E-02	0.600+/-0.072	0.0001
RI-Left ICA	0.744+/-7.544E-02	0.600+/-0.085	0.0001

Student's t-test. All reported P values are two-sided.
SD-standard deviation, SBP-systolic blood pressure, DBP-diastolic blood pressure, GFR-glomerular filtration rate, RI-resistance index, MCA-middle cerebral artery, ICA- internal carotid artery, CKD-chronic kidney disease.

Table 2. Types of cerebral vascular lesions in CKD (+) and CKD (-) patients.

Variable	CKD (+)n=418	CKD (-)n=172	P
Diffuse CA+MCA atherosclerosis	79.7%	91.9%	0.0001
CA stenosis	10.0%	4.1%	0.0001
CA occlusions	5.3%	2.3%	0.0001
CA stenoses+occlusions	1.2%	0.6%	0.0001
CA multiple stenosis	3.8%	1.1%	0.0001

Chi-square test. All reported P values are two-sided.
ECD- extracranial Doppler ultrasound, TCD- transcranial Doppler ultrasound, CKD- chronic kidney disease, CA- carotid artery, MCA-middle cerebral artery.

Table 3. Types of ischaemic cerebrovascular disease in relationship with the vascular territories in CKD(+) and CKD(-) patients.

Type of cerebrovascular disease according to the vascular territory	CKD (+)n=418	CKD (-)n=172	P
Lacunar infarction	20.1%	28.5%	0.042
VB TIA	8.9%	16.3%	0.0001
Right ICA TIA	3.6%	5.8%	0.001
Left ICA TIA	11.7%	5.2%	0.0001
VB infarction	6.7%	7.0%	0.042
Right MCA infarction	23.4%	14.5%	0.0001
Left MCA infarction	25.6%	22.7%	0.036

Chi-square test. All reported P values are two-sided. Significance was considered as $P<0.05$.
VB- vertebro-basilar, TIA- transient ischaemic attack, ICA-internal carotid artery, MCA-middle cerebral artery, CKD- chronic kidney disease.

Table 4. Risk factors for localized cerebral vessels lesions (stenoses and occlusions) vs. diffuse atherosclerosis within the CKD(+) group.

Parameter	OR	95.0 % C.I. for OR		P
		Lower	Upper	
C-reactive protein	2.28	1.146	2.544	0.001
Proteinuria	2.26	1.134	2.510	0.001
Haemoglobin	0.26	0.134	0.510	0.0001
Sex(male)	2.01	1.243	3.265	0.004
Age(older)	0.93	0.911	0.959	0.0001

Multivariate logistic regression analysis-parsimonious model. Odds ratios (ORs) and their 95% confidence intervals (CI) were calculated. All P values were calculated based on two-sided statistical tests. Significance was considered as P<0.05.

Table 6. Correlations between risk factors and the resistance indices in the middle cerebral arteries in CKD(+) patients.

Variable	Standardized ß coefficients	P
Fibrinogen	0.050	0.05
C-reactive protein	0.273	0.0001
GFR	-0.645	0.0001

R= 0.898; R-square=0.806; F=417.002; P<0.001
Correlations between risk factors for modified cerebral vessels and the resistance index in the right middle cerebral artery (MCA) were evaluated by multiple regression analysis. CKD-chronic kidney disease, GFR-glomerular filtration rate; Dependent variable: RI-right MCA.

hemoglobin (*P*<0.040), proteinuria (*P*<0.001), male gender (*P*<0.009), and older age (*P*<0.0001) were the significant independent variables. In the parsimonious model remained only C-reactive protein (*P*<0.001), proteinuria (*P*<0.001), hemoglobin (*P*<0.0001), male gender (*P*<0.004), and older age (*P*<0.0001) (Table 4).

In CKD (+) patients the RI in the ICA_s correlated with fibrinogen (*P*<0.0001) and GFR (*P*<0.0001) (Table 5), while the RI in the MCA_s correlated with fibrinogen (*P*<0.05), C-reactive protein (*P*<0.0001), and GFR (*P*<0.0001) (Table 6). No correlation was found between diffuse cerebral vascular changes and the CKD stage (*P*=0.671), nor between grades of stenosis and CKD stage (*P*=0.343), evaluated by the Spearman Rank Order test.

4. Discussion

Our study attempted to evaluate the prevalence of CKD in patients with symptomatic ischemic cerebrovascular disease and to establish of whether CKD may define a particular risk pattern for pathological modifications of cerebral vessels in this category of patients. In our study we demonstrated an increased prevalence of CKD in patients with ischemic cerebrovascular was very significant even for early stages of CKD (stages 1-3).

Table 5. Correlations between risk factors and the resistance indices in the internal carotid arteries in CKD(+) patients.

Variable	Standardized ß coefficients	P
Fibrinogen	0.280	0.0001
GFR	-0.624	0.0001

R= 0.882; R-square= 0.778; F=528.581; P<0.001
Correlations between risk factors for cerebral vessels modifications and the resistance index in the right internal carotid artery (ICA) were evaluated by multivariate regression analysis. CKD-chronic kidney disease, GFR-glomerular fitration rate; Dependent variable: RI-right ICA.

Neither both the prevalence of stenosis and occlusions in the carotid arteries, nor the grades of stenosis correlated with the CKD stages, a fact which shows that severe vascular lesions may be recorded irrespective of the CKD stage, and as such even early stages of CKD may be associated to important cerebral vessels atherosclerotic and arteriosclerotic modifications.

A pooled analysis of community-based studies performed in the general population (Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study) showed that CKD was an independent risk factor for the composite study outcome, including stroke. In patients with GFR of 15-59 ml/min, the prevalence of stroke (% events) was 7.5%, while in patients with GFR≥60 ml/min, the prevalence of stroke was 2.8% [7]. The increased prevalence of CKD in our study by comparison with other reports about in-hospital patients might have been related to the fact that the study included only patients with proved important cerebral vessels modifications.

Mild degrees of renal dysfunction are associated with increased risk of incident ischemic stroke or TIA in patients with pre-existing atherothrombotic disease. Therefore, patients with renal dysfunction should be considered as a high-risk group for cardiovascular disease and ischemic stroke [8]. Impaired kidney function is associated with markers of cerebral small vessel disease, as assessed on MRI [9].

4.1. Cerebral vessels modifications

Atherosclerosis and arteriosclerosis are the most frequent cerebral vascular lesions described in patients with CKD.

In our study, data provided by ECD and TCD showed a predominance of diffuse atherosclerotic modifications in the carotid arteries and middle cerebral arteries in patients without CKD, whereas more severe, localized lesions were described in patients with CKD, namely stenosis, occlusions, combined stenosis and occlusions, and multiple stenosis of the carotid arteries.

The vast majority of the imaging methods which assess cerebrovascular modifications in pre-dialysis and haemodialysis patients rely on B-mode echo Doppler in which intima-media thickness (IMT) is the utilized index to evaluate the morphology of the vessel wall. As an additional functional index of this method, pulse wave velocity is utilized for the assessment of vascular stiffness [10-12].

Very sensitive indices for the accurate diagnosis of morphological and functional modifications in the cerebral vessels are the pulsatility index (PI) and the resistance index (RI), evaluated by ECD in the ICA_s and by TCD in the MCA_s and the vertebro-basilar territory [13].

In our study the RIs found by neurosonology were significantly increased, closely related to the severity of the cerebral vessels lesions in patients with symptomatic ischemic cerebrovascular disease and CKD. It is assumed that parameters of ECD, such as pulse wave velocity, IP, and IR are more relevant for the increase in the stiffness of the vessel walls and for the decrease in their compliance and distensibility. These parameters are highly predictive of mortality through cardiovascular complications in haemodialysis patients [14]. Mourad J. et al., by evaluating the pulse wave velocity in the common carotid artery in young patients (under the age of 50 years) with the renal function at the upper limit of the normal range or with mild renal to moderate decline in renal function (as estimated by the creatinine clearance), showed a significant increase in the rigidity of the vessel wall and a decrease in its compliance [15]. Also, carotid arterial wall stiffness is increased in young adult patients with paediatric ESRD. Hypertension is a main determinant and might be a target for treatment of these life-threatening arterial wall changes [16].

Moreover, ECD and TCD ultrasound, by utilizing the PI and RI, proved a reliable tool in the assessment of structural and functional changes in the cerebral vessels in asymptomatic non-diabetic and diabetic CKD patients, modifications which correlated with classic and non-classic cerebrovascular risk factors [17-22].

Although the differences concerning the topographic diagnosis of the ischemic cerebrovascular disease were significant in CKD (+) patients vs. CKD (-) patients, we could not find any explanation for this data. The literature consulted failed to provide additional data with regard to this particular issue found in CKD patients.

Cerebrovascular lesions reflect the extension of atherosclerotic lesions in various vascular beds, and emphasize the fact that patients with both stroke and renal function impairment have an increased cardiovascular morbidity and mortality [23]. Due to similarities in the vascular supply to the kidney and brain, vascular disease in one organ may share common risk factors with vascular disease in the other [24].

Similar data was found in our study in CKD (+) patients, which points to the fact that the great majority of CKD patients might overlap multiple vascular lesions in critical vascular territories, such as the coronary and peripheral arteries.

A study conducted in CKD patients disclosed the fact that all CKD patients with PVD and 86% of the patients with CHD had carotid artery lesions [25]. Kawagishi T. et al. showed that haemodialysis patients presented advanced atherosclerosis in the carotid and femoral arteries when compared with age-matched healthy control subjects [26]. The same results were reported by Savage T. et al. in dialysed patients who displayed a strong association between carotid artery lesions and femoral artery atherosclerosis [27].

Compound atherosclerosis and calcinosis lesions were detected by ultrasonography in both, carotid and femoral arteries in early stages of CKD and progression of their severity was proportional to renal function decline [28].

4.2. Risk factors for cerebrovascular remodelling

Risk factors for cerebral vessels are shared by cerebrovascular disease and CKD as well.

Irrespective of age, male gender was an important risk factor in CKD (+) patients, data which is in keeping with several studies [25,26,29]. Hypertension is one of the most significant factors involved in the hypertrophy-type of the cerebral vessels, irrespective of the level of renal function impairment [30]. Hypertension was present in the vast majority of the cases with CKD in our study group. Some authors underline the fact that the high levels of SBP are a strong predictor of severe and extensive atherosclerotic lesions than are those of DBP [29], while other authors state that neither the levels, nor the duration of hypertension are of predictive value [25,26]. Hypertension plays an important role in the occurrence of silent brain infarction (a small vessel disease of the brain). This fact is more prominent in patients with CKD and is indicative of a cerebro-renal association, thus establishing a link between vascular disease of the kidney and the brain [31].

Lipid abnormalities concerning increased cholesterol and triglycerides levels were also very significant in CKD (+) patients. Commonly, patients with severe cerebral vessels lesions have elevated levels of total cholesterol, LDL-cholesterol and triglycerides, while the levels of HDL-cholesterol are low [25,26,29]. Carotid arterial changes occur early in the course of

CKD and may be related to dyslipidaemia of the early stages [32].

Markers of inflammation, such as fibrinogen and C-reactive protein have been proved important contributors to the elevated risk for stroke in CKD(+) patients as compared to CKD (-) patients. Both parameters have been found to be independently associated with the cerebrovascular risk, but also with the level of renal function decline [33,34]. Moreover, even in silent cerebral lacunae, fibrinogen proved to be an important risk factor [35].

In our study, the RIs in the sonorized arteries correlated significantly with the parameters of inflammation, a fact which is indicative of their role in the occurrence of atherosclerosis and arteriosclerosis. Similar results were found in another study performed by us in asymptomatic CKD patients, in whom the Doppler indices correlated with the two markers of inflammation [18].

In our study, proteinuria was significantly increased in CKD (+) patients when compared to CKD (-) patients. Elevated urinary albumin excretion has been demonstrated as an independent risk factor for CKD, as well as for cardiovascular complications, including stroke [33]. Microalbuminuria has been shown to be a predictor of ischemic stroke, a fact related, in part, to an increased carotid intima-media thickness, which means carotid atherosclerosis and a strong association with cerebrovascular damage, either symptomatic or asymptomatic [36]. Individuals with proteinuria combined with increased levels of serum creatinine and/or reduced GFR run the risk for stroke, thus demonstrating that the prominent risk factors potentiate their causal effect [37,38].

In our patients with CKD, GFR was an independent risk factor for cerebral vessel modifications and correlated significantly with the RI assessed in the ICA_S and MCA_S. Decreased renal function is a risk factor for increased carotid intima-media thickness [35]. CKD may potentiate non-traditional cardiovascular risk factors, reduced kidney function may be a marker for both duration and severity of other causes of cardiovascular disease, and patients with CKD are withheld more aggressive cardio- and neuroprotective measures [7,38].

In our study, low levels of were an important risk factor for cerebral in CKD (+) patients as compared to CKD (-) patients. Our patients with levels >11g/dl seemed to be more protected against severe vascular lesions and subsequent extensive ischemia in the corresponding vascular territories. A level of <9g/dl is associated with an increase of 22% in the risk for stroke [39]. The mechanisms through which anemia is instrumental in the occurrence of stroke are represented by the direct consequences of hypoxia on the hypoperfused cerebral territories which are extended in CKD patients, and by the effects of on cardiac and arterial hypertrophy. Chronic increase in cardiac output secondary to leads to the elastic-type arteries, including common carotid arteries. This consists of vascular dilatation, and increase in intima-media thickness and in the rigidity of the vessel wall [40]. The combination of CKD and anemia was associated with a substantial increase in stroke risk, independent of other known risk factors for stroke, in a middle-aged, community-based population included in the ARIC study [41].

In conclusion, our study performed in patients with symptomatic ischemic cerebrovascular disease assessed by ECD and TCD ultrasound shows a high prevalence of CKD in patients with important atherosclerotic and arteriosclerotic cerebral vessels modifications. There is a strong relation between symptomatic cerebrovascular disease and CKD, a fact demonstrated by the increased prevalence of CKD in these patients and by the severity of the cerebral vessels lesions, even in its early stages. Risk factors for this particular pattern of cerebral vessels modifications were markers of inflammation, proteinuria, anaemia, and GFR. These cerebral vessels changes were associated with similar lesions in other vascular beds, such as the coronary and peripheral arteries.

Moreover, our study supports the fact that the neurosonographic methods are reliable and non-invasive, useful in the detection of cerebral vessels modifications in CKD patients. These methods have a predictive value in the diagnosis of similar vascular changes in other vascular beds and may be utilised safely in patients with renal function impairment, in whom contrast-enhanced imaging methods should be indicated only in selected cases.

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