



Relationship between chronic kidney disease and cerebral white matter hyperintensities: a systematic review

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Background: This systematic review summarizes available evidence on the relationship between white matter hyperintensities (WMH) volumetric quantification on brain MRI scans and chronic kidney disease (CKD).

Methods: The literature search was performed in March 2022 using MEDLINE PubMed Central, Scopus and Web of Science – Publons as search engines. Relevant articles investigating, with a quantitative volumetric approach, the link between WMH and CKD patients were selected.

Results: The database search strategy found 987 articles, after excluding duplicates, the titles and abstracts of the remaining 320 articles were examined. Subsequently 276 articles were excluded as they were not relevant to the topic. Of the 44 articles evaluated for eligibility, 36 were excluded because the quantitative analysis of WMH was not volumetric. Finally, 8 articles were included in this systematic review.

Conclusions: Literature on this topic is extremely heterogeneous in terms of methodology and samples. However, evidence shows that there is a relationship between CKD and WMH volume of the brain. We recommend that quantifiable biomarkers such as estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (UACR) should be included in studies dealing with cerebrovascular disease. The biological and molecular mechanisms underlying cerebrovascular damage in patients with chronic renal failure deserve to be further explored.

Keywords: Brain magnetic resonance imaging (brain MRI); chronic kidney disease (CKD); chronic renal failure; small vessel disease; white matter hyperintensities (WMH)

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Introduction

The kidneys can be affected by a wide range of disease conditions including oncological, infectious, traumatic, and degenerative disorders (1-4).

Chronic kidney disease (CKD), also known as chronic kidney failure, is characterized by progressive tissue damage and gradual loss of kidney function. CKD is a common pathological condition and is most frequently encountered in elderly individuals. Diabetes and hypertension are the main causes of CKD in both developed and developing countries; glomerulonephritis and unknown causes are more common in countries of sub-Saharan Africa and Asia (5).

In the early stages, there may be few signs or symptoms, but when the condition becomes more advanced, CKD can exhibit systemic effects beyond the kidneys. Intriguingly, a relationship between renal function and brain structural alterations has been suggested (6). Indeed, CKD-related indicators such as albuminuria and reduced estimated glomerular filtration rate (eGFR) are considered risk factors for stroke, dementia, and death (7,8).

Computed tomography (CT) and magnetic resonance imaging (MRI) are non-invasive tools for qualitative and quantitative assessment of tissues (9-13). On T2-weighted turbo spin echo (TSE) or fluid-attenuated inversion recovery (FLAIR) cerebral MRI scans, scattered or confluent white matter hyperintensities (WMH) are commonly observed, especially in elderly individuals (14-16). These are known as a marker of cerebral small vessel disease and have been linked to an increased risk of stroke, dementia, and death (14-16).

A recent meta-analysis of 16 case-control studies found that subjects with an eGFR <60 mL/min/1.73 m² (stage 3 CKD or moderate CKD) show an increased incidence of WMH compared to subjects with an eGFR >60 mL/min/1.73 m² (17). Moreover, cross-sectional observational studies have found a correlation between WMH volumes, quantified using automated techniques, and urinary albumin levels (18,19).

Many studies have assessed WMH using the Fazekas scale, a semi-quantitative, non-volumetric method, proposed by Fazekas *et al.* in 1987, to simply describe the amount of cerebral white matter T2 hyperintense lesions (20). The Fazekas scale divides the white matter into the two regions, periventricular and deep white matter; each region is graded according to the size and confluence of the lesions (*Figure 1*) (20).

Another approach to measure WMH is the volumetric

quantification, which tends to be less subjective, more sensitive, and effective (21-23).

The present systematic review focuses on WMH distribution and volumetric quantification in patients with chronic renal failure. The aim of this paper is to evaluate the available evidence about the impact of chronic renal failure on brain health as evaluated by means of MRI-based volumetric analysis of WMH.

Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (24,25), the PRISMA reporting checklist is available at <https://qims.amegroups.com/article/view/10.21037/qims-22-707/rc>.

Search strategy

The literature search was carried out in March 2022 using MEDLINE PubMed Central, Scopus, and Web of Science – Publons. Only articles written in English, without limits of time span, were included. The keywords used for articles search were: “renal failure white matter hyperintensities”, “chronic renal failure white matter hyperintensities”, “chronic kidney disease white matter hyperintensities”, “end stage renal disease white matter hyperintensities”, “renal insufficiency white matter hyperintensities” and “renal dysfunction white matter hyperintensities”.

Eligibility criteria

The eligibility criteria were based on study design and on the method of analysis of WMH. Articles included were focused on the association between chronic renal failure and WMH performed by volumetric analysis. Therefore, studies assessing chronic renal failure and non-volumetric WMH analysis (e.g., Fazekas scale), were excluded. Cross-sectional, prospective cohort and retrospective studies were included. No limit was set on the aim of the studies.

Data extraction and risk of bias assessment

Two reviewers independently performed the search (FG and CAM). All peer-reviewed journals were screened, and all relevant studies were explored. The first step was to rule out duplicates. All the titles and abstracts were then evaluated considering the inclusion criteria by two authors

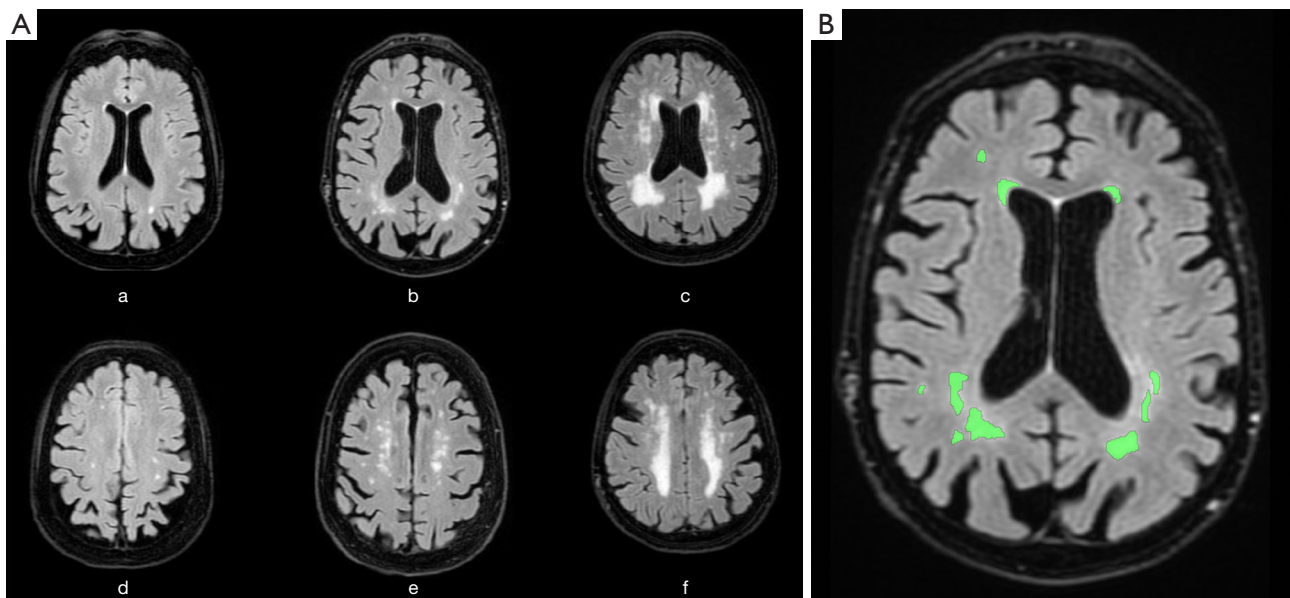


Figure 1 (A) Non-volumetric assessment of cerebral WMH using the Fazekas scale, illustrating Grades 1, 2 and 3 in the periventricular region (a, b and c respectively) and in the deep white matter (d, e and f respectively). Periventricular white matter: 0= absent; 1= “caps” or pencil-thin lining; 2= smooth “halo”; 3= irregular periventricular signal extending into the deep white matter. Deep white matter: 0= absent; 1= punctate foci; 2= beginning confluence; 3= large confluent areas. (B) Volumetric assessment of WMH through segmentation on axial FLAIR image. Single-slice ROIs containing pixels of WMH are illustrated in green. These ROIs are drawn on a slice-by-slice basis, allowing for the volumetric quantification of the entire WMH. WMH, white matter hyperintensities; ROIs, regions of interest.

(FG and CAM). Full text was evaluated when the title and abstract did not provide adequate information regarding the inclusion criteria.

Disagreement regarding the inclusion or exclusion of an article was assessed through discussion between the two reviewers (FG and CAM), until a consensus was reached. In no cases was there a need for the opinion of a third reviewer.

The estimation of the potential bias was performed using assessment criteria established by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (26).

To avoid inaccuracies and inconsistencies, selected articles were evaluated independently by two reviewers (FG and CAM).

Results

The database search strategy yielded 987 articles (Figure 2). After removal of duplicates, the titles, and abstracts of the remaining 320 articles were scrutinized. Consequently, 276 articles were excluded as the abstract and title were not relevant to the topic of this systematic review.

Of the 44 articles assessed for eligibility, 36 were excluded as the quantitative analysis of WMH was not a volumetric analysis. Finally, 8 articles were included in the systematic review. Most of these studies showed a level of evidence of 1. For the results summary of the individual studies please see Table 1.

The estimation of potential risk of bias is summarized in Figure 3.

Discussion

The (potential) link between cerebral WMH volume and chronic renal failure has been an interesting research target in recent years. Several studies have attempted to fill this knowledge gap. The major indicators of CKD applied in such studies were creatinine clearance, serum creatinine, eGFR, and UACR.

Creatinine clearance and white matter hyperintensities volume

Of note is the Northern Manhattan Study in a community-

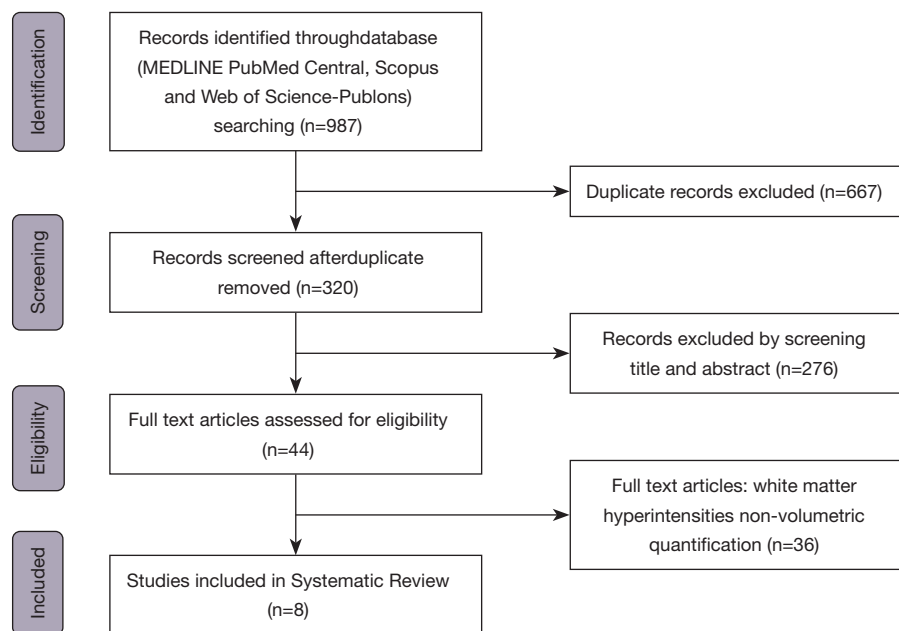


Figure 2 Search mode flow diagram according to the PRISMA protocol. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

based cohort of stroke-free subjects undergoing MRI (26). In this study, published in 2007, the authors performed volumetric analysis of cerebral WMH through an MRI-based approach. The relationship between renal function and log-WMH volume adjusted for gender, age, race-ethnicity, cardiac disease, homocysteine, hypertension, diabetes, and education was assessed using linear regression. A cohort of 615 subjects with an average age of 70 years were enrolled. Multivariate analysis showed a relationship between creatinine clearance 15 to 60 mL/min and increased log-WMH volume ($\beta = 0.322$; 95% CI: 0.095 to 0.550). Interestingly, increased creatinine per 1-mg/dL showed a positive correlation with log-WMH volume ($\beta = 1,479$; 95% CI: 1,067 to 2,050). This association highlights the importance of kidney disease as a determinant of cerebrovascular damage and/or as a biomarker for microangiopathy (27).

Serum creatinine, glomerular filtration rate and white matter hyperintensities volume

Another large study by Turner *et al.* investigated the relationship between serum creatinine and cerebral small vessel arteriosclerosis assessed by quantifying the WMH volume on brain MRI and with peripheral large vessel

arteriosclerosis determined by the ankle-brachial index (28). Sibling members (804 Caucasians and 781 Afro-Americans) of whom at least two siblings had primary hypertension, were enrolled in the study. After adjusting for age, the authors found an increase in serum creatinine with greater WMH volume (correlation coefficient of 0.5) and with decreased ankle-brachial index (0.50; $P < 0.001$) (28).

The relationship between biomarkers of renal function and gray matter volume, cerebrovascular conditions (i.e., WMH, cerebral infarctions, micro-hemorrhages), and microstructural changes assessed by brain MRI in CKD patients was investigated by Vemuri *et al.* (29). Volumetric quantification of WMH was performed using an automated method on FLAIR images. Diffusion tensor imaging was used for the evaluation of white matter microstructural changes. Urine albumin to creatinine ratio (UACR) and eGFR joint models including both predictors were adjusted for vascular risk factors by linear regression. The 240 brain MRI scans analyzed showed higher WMH volume, a greater likelihood of cortical infarcts, and worsening of diffusion changes throughout the brain in subjects with lower eGFR. In the analysis adjusted with the regression model a 10% decrease in and GFR was associated with a 2.8% increase in WMH volume, in the joint model was detected at trend level effects of eGFR ($P = 0.09$) (29).

Table 1 Summary of studies evaluating the correlation between CKD parameters and WMH volume

Authors	CKD parameters	WMH data	Brain MRI sequence	WMH quantification software	Number of subjects	Results	Level of evidence*
Khatri <i>et al.</i> , 2007 (27)	Serum creatinine; creatinine clearance; eGFR	Log-WMH volume	FLAIR	Quantum 6.2 package on a Sun Microsystems Ultra 5 workstation	615	Creatinine clearance: P<0.001; eGFR: P<0.001	3
Turner <i>et al.</i> , 2011 (28)	Serum creatinine; UACR	WMH volume	FLAIR	Not specified	1,585	Serum creatinine correlation coefficient: 0.54; UACR correlation coefficient: 0.52	3
Vemuri <i>et al.</i> , 2017 (29)	eGFR; UACR	WMH volume	FLAIR	Statistical Parametric Mapping	240	eGFR: P=0.002; UACR: P<0.001	1
Bronas <i>et al.</i> , 2019 (30)	eGFR	WMH volume	BRAVO; FLAIR	Support vector machine classifier	94	eGFR: b=0.009	1
Marini <i>et al.</i> , 2020 (31)	eGFR; UACR; pleiotropic locus 2q33; other pleiotropic loci	WMH volume	T1 FLAIR; T2 FLAIR	Summary statistics of GWAS analysis for total volume of WMH derived by the UK Biobank study	10,597	eGFR: P=0.177; UACR: P=0.020; 3 pleiotropic locus 2q33 posterior probabilities of association of 0.80; no statistically significant correlations with other pleiotropic loci	3
Yamasaki <i>et al.</i> , 2020 (32)	eGFR; UACR	IC volume-corrected WMH volume	T1-weighted FLAIR	LST for SPM12	1,214	No statistically significant correlation for eGFR; UACR: P=0.01	1
Vemuri <i>et al.</i> , 2021 (33)	eGFR; UACR	WMH volume	FLAIR	Statistical Parametric Mapping	242	No statistically significant correlations for eGFR and UACR	1
Bijkerk <i>et al.</i> , 2022 (34)	Angiotensin-2 Asymmetric dimethylarginine miR-27a; miR-29a; miR-126; miR-132; miR-137; miR-192; miR-223; miR-326	WMH volume	Not specified	Quantib brain, Rotterdam, the Netherlands	70	Angiotensin-2: P=0.016; no statistically significant correlations with the remaining data	1

*, SIGN100: Scottish Intercollegiate Guidelines Network 2019. CKD, chronic kidney disease; WMH, white matter hyperintensities; MRI, magnetic resonance imaging; eGFR, estimated glomerular filtration rate; FLAIR, fluid-attenuated inversion; UACR, urine albumin to creatinine ratio; BRAVO, axial MRI 3D brain volume; LST, Lesion Segmentation Toolbox.

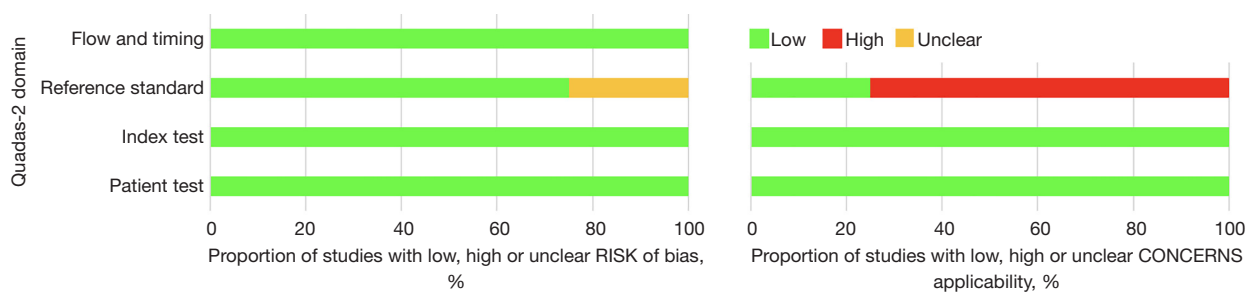


Figure 3 Summary of the methodological quality of the QUADAS-2 score by assessing risk of bias and applicability concerns. High, low, and unclear risks of bias are represented in red, green, and yellow respectively. Higher proportion of studies with concerns regarding applicability was found, due to differences in diagnostic technology, execution, or interpretation, possibly influencing diagnostic accuracy. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies.

Bronas *et al.* analyzed indicators of impaired renal function, sedentary time and WMH in 94 healthy non-demented and non-depressed adults (30). Renal function was evaluated with the epi-CKD formula for eGFR. WMH volumes quantification was performed by affine registration of the T1-weighted axial MRI 3D brain volume (BRAVO) data to the T2-weighted FLAIR data. WMH volumes were segmented automatically and corrected by the participant's corresponding intracranial volume to account for individual differences in head size. This led to a measurement of the WMH volumes as a percentage of the intracranial volume.

Adjusting for age, sex, education, Framingham stroke risk 10-year prediction score, sedentary attitude was related to increased WMH volume, but this effect depended upon eGFR (sedentary time * eGFR interaction $b=-0.0005$, $P=0.022$). At eGFR 25th, 50th, and 75th percentiles, sedentary time b coefficients were $b=0.021$ (95% CI: 0.011–0.031), $b=0.015$ (95% CI: 0.008–0.022), and $b=0.009$ (95% CI: 0.003–0.016). The results of this study suggest that sedentary time is associated with WMH volumes in persons with an eGFR ≤ 96 mL/min/1.73 m² and that this relation is stronger with lower levels of renal function (30). Sedentary time may impair vascular brain function by increasing inflammation and oxidative stress and reducing angiogenesis, neurogenesis and/or synaptogenesis (35).

Marini *et al.* reported genetic data aimed to identify a correlation between impaired renal function and phenotypes of cerebrovascular diseases (31). Summary statistics from genome-wide association studies of renal function traits (CKD diagnosis, eGFR, UACR) and cerebrovascular disease phenotypes (i.e., ischemic stroke and respective subtypes, intracerebral hemorrhage, and WMH on brain MRI) were used. WMH volume was analyzed using summary statistics of genome-wide association studies analysis for WMH volume derived by the UK Biobank study. Volumetric analysis was performed on a very large sample of 10597 participants of European ancestry using T1 and T2 FLAIR images. Sex, age and principal components were used for adjusting linear regression model of the genome-wide association studies. Polygenic risk score for lower eGFR was related with higher large artery stroke risk ($P=1 \times 10^{-4}$). Pleiotropic locus 12q24 was associated with eGFR and both large artery stroke and small vessel stroke. Moreover, mendelian randomization demonstrated a correlation with lower eGFR [odds ratio for 1-log decrement (1-log decrease the value to the power of 1), 2.10; 95% CI: 1.38–3.21] and higher UACR [odds ratio per 1-log increment (1-log increment the value to the power of 1), 2.35; 95% CI: 1.12–

4.94], with a higher risk of large artery stroke. It should be highlighted that this study showed, on a very large sample, the genetic relationship between impaired renal function and cerebrovascular pathologies across the genome and pleiotropic loci. Impaired hemofiltration and glomerular function appear to play a causal role in stroke, possibly contributing to the greater atherosclerosis. The authors also showed that the pleiotropic locus 2q33 may play a role in pathologies of the small vessels of the kidney and brain through microalbuminuria, small vessel stroke and WMH. This locus encodes the ICA1L, WDR12, and NBEAL1 genes and have been linked to both small vessel stroke risk and WMH (31). This study suggested a common genetic fingerprint between CKD and WMH volume. Pleiotropic analysis across the 12q24.12 locus showed an association between eGFR and the risk of large artery stroke. In particular, the mutation of the SH2B3 gene, found in this locus, has been associated with high blood pressure, a known risk factor for both stroke and kidney disease, which could explain part of the shared gene predisposition between the two entities (36).

Yamasaki *et al.* investigated the association between albuminuria and WMH in elderly Japanese (32). Japanese subjects ($n=1,214$) aged ≥ 65 years underwent brain MRI to evaluate WMH volume together intracranial volume ratio (i.e., IC volume-corrected WMH volume). T1-weighted and FLAIR images were used for the quantification of WMH volume. IC volume-corrected WMH volume was associated with eGFR without detecting any correlation between the two parameters (32).

A further study by Vemuri and colleagues assessed the impact that CKD can have on brain health through correlations between eGFR and cortical thickness, ventricular volume, WMH volume and fractional anisotropy of the corpus callosum on 242 subjects using longitudinal imaging (33). Cortical thickness and ventricular volume were quantified on MPRAGE images, while WMH volume was measured on FLAIR images by semi-automatic segmentation. The authors considered fraction anisotropy in the corpus callosum as diffusor tensor imaging metric because it is an important anatomical structure for cognitive performance and is influenced by vascular health. The results showed an increased WMH volume and a decreased anisotropy fraction in corpus callosum in CKD participants (both $P < 0.001$). Once again, another study demonstrating the relationship between renal function (i.e., eGFR) and white matter damage in CKD patients (33). These results support the hypothesis that CKD progression affects

cognitive function at least partially by means of small vessel disease-related mechanisms. White matter changes found in aging and dementia are usually due to small vessel disease in the elderly. Relative causes are variable and include hypoperfusion, blood-brain barrier dysfunction, altered water content, myelin damage, and axonal disruption (37).

Lastly, a very recent study by Bijkerk *et al.* investigated the relationship between levels of Angiopoietin-2, asymmetric dimethylarginine, circulating angiogenic miRNAs (i.e., miR-27a, miR-29a, miR-126, miR-132, miR-137, miR-192, miR-223 and miR-326) and small vessel disease together with cognitive impairment in 129 end stage renal disease older patients (mean age 75.3 years; mean eGFR 16.4 mL/min). Changes in small vessel disease (WMH volume, microbleeds and lacunes) were evaluated by brain MRI, while neuropsychological tests were used to evaluate cognition in domains of memory, executive functions, and psychomotor speed (34). Brain MRI was available on 70 of 129 enrolled patients, WMH volume was quantified using an automated method after manually segmenting other pathologies. Furthermore, WMH were assessed using the Scheltens scale, which is considered a more detailed visual scale than the Fazekas scale, while lacunes and microbleeds were evaluated using the STRIVE criteria (38,39). Angiopoietin-2 showed a correlation with small vessel disease, both with WMH volume ($P=0.016$) and with the Scheltens score ($P=0.08$). Furthermore, angiopoietin-2 showed a statistically significant correlation with executive function and psychomotor speed, while miR-223 and miR-29a showed an association with memory functions. These angiogenic markers could be used to identify the risk of cerebral small vessel disease and cognitive decline in patients with end stage renal disease (34).

Urine albumin to creatinine ratio and white matter hyperintensities volume

Turner *et al.* evaluated the relationship between UACR and cerebral small vessel arteriosclerosis, finding a correlation between the increase in UACR with the increase in WMH volume (correlation coefficient of 0.52) and with decreased ankle-brachial index (0.54; $P<0.001$) (28). This study offered additional evidence on the link between CKD and WMH volume (28).

The correlation between the WMH volume calculated on 240 brain MRI scans and the UACR performed by Vemuri *et al.* showed a link between these two parameters.

In particular in the analysis adjusted with the regression model a 10% increase in UACR was associated with a 0.32% increase in WMH volume, In the joint model the effect of UACR was significant ($P=0.09$) (29). The importance of this study is also highlighted by the higher number of MRI-based brain variables evaluated and by the demonstration of the relationship between CKD and cerebrovascular pathologies together with microstructural brain changes (29).

The analysis performed by Marini *et al.* between UACR and cerebrovascular disease phenotypes found a correlation between the Pleiotropic locus 2q33 with UACR and both small vessel stroke and WMH volume. While mendelian randomization demonstrated a correlation with higher UACR (odds ratio per 1-log increment, 2.35; 95% CI: 1.12–4.94), with a higher risk of large artery stroke and greater risk of intracerebral hemorrhage (31).

The correlation between IC volume-corrected WMH volume with UACR performed by Yamasaki *et al.* was associated with cognitive decline and mortality risk. The whole population showed a geometric mean of IC volume-corrected WMH volume ratio of 0.223%. This geometric mean increased significantly with greater UACR after adjusting for confounding factors (0.213% with normoalbuminuria, 0.248% with microalbuminuria, and 0.332% with macroalbuminuria; $P_{\text{trend}}=0.01$). Moreover, subjects with albuminuria and higher IC volume-corrected WMH volume [$\geq 0.257\%$ (median)] were more likely to develop cognitive decline at baseline or all-cause death during follow-up than subjects with normal albuminuria and low IC volume-corrected WMH volume [$< 0.257\%$ (median)]. This evidence highlighted that elevated albuminuria levels are associated with larger WMH volume in an elderly Japanese population. Albuminuria levels were related to WMH enlargement with the increased risk of cognitive decline and all-cause mortality suggesting that urinary albumin levels may be useful for WMH risk assessment, and can be critical in the prevention of stroke, dementia, end-stage renal failure and death (32).

Albuminuria can be a marker of risk factors for WMH such as hypertension and diabetes, but also of endothelial dysfunction in the kidney (40). The brain and kidney are hemodynamically similar since they are perfused by small vessels directly arising from large blood vessels and thus are perfused by large amounts of blood with low vascular resistance (41,42). In this way, these two organs are vulnerable to vascular damage when exposed to high pressure (41,42).

The study conducted by Vemuri *et al.* found no correlation between the increase in UACR and changes in WMH volume (33).

Future perspectives

A novel and interesting concept that is being studied is that the brain can be affected by systemic conditions or disorders, such as in the case of CKD. The literature is still sparse and available studies on the topic are extremely heterogeneous in terms of methodology and samples. However, evidence is accumulating that abnormal function of the abdominal organs, such as the kidney, can affect the brain and be related to cerebral small vessel disease and be associated to an increased WMH volume load. This is likely mediated by accumulation of circulating substances possibly exhibiting toxic effects on small vessels and white matter of the brain. However, additional effort is needed to improve standardization of methodologies across studies, to increase the accuracy with different techniques to analyze brain activity such as functional MRI and electroencephalography, and to understand the impact of CKD on the risk of developing various brain diseases such as neurodegenerative disorders (43-45).

Moreover, hypertension and diabetes, risk factors for CKD, can also cause microstructural and macrostructural damage to the white matter. Hypertension is considered a classic risk factor for WMH. Indeed, a Biobank cohort study demonstrated a linear association between neuroimaging biomarkers (i.e., WMH volume and diffusion imaging indices) and mean arterial and pulse pressures (46). In addition to hypertension, many studies suggest that diabetes mellitus may be associated with WMH progression and, furthermore, insulin resistance is thought to be an exacerbating factor along with other risk factors such as dyslipidemia, smoking, or other vascular risk factors (47,48).

This systematic review found no studies that performed the volumetric analysis of WMH in CKD dialysis patients. The link between WMH and CKD in dialysis patients compared to healthy subjects is known (49). Further studies would be helpful to quantify WMH in dialysis patients by means of volumetric analysis and better define the relationship among CKD, dialysis and WMH. Furthermore, it would be interesting to assess with future systematic reviews and meta-analyses studies dealing with the relationship between CKD and the full spectrum of cerebral small vessel diseases in order to better understand the underlying pathogenetic mechanisms.

Conclusions

Our systematic review reveals that the literature on the topic of CKD and WMH volume is quite heterogeneous. Despite this heterogeneity, we found evidence that there is a clear link between CKD and cerebral WMH volume. Our finding implies that, in all studies regarding cerebral WMH imaging findings, it is of great importance to take renal function into consideration. Data such as eGFR and UACR should be included as variables to better understand the pathogenesis of cerebral WMH, and to identify patients with CKD at the risk of cerebrovascular disease. The progressive decline in glomerular filtration rate in CKD patients causes a wide range of physiological, biochemical and hematological changes which may impact the cerebral blood vessels and particularly the microvascular environment in the white matter. These biological and molecular mechanisms underlying cerebrovascular damage in patients with chronic renal failure deserve to be further explored.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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