Original Research Article

Correlation of Silent Brain Infarction with the Metabolic Abnormality of CKD Stage 3-5 (*non-dialytic*) Patients

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Abstract: *Background*: Silent brain infarction (SBI) poses a significant yet often undetected risk in chronic kidney disease (CKD) patients, predisposing them to symptomatic stroke, dementia, and neurological mortality. Despite its implications, the association between SBI and CKD remains elusive, necessitating further exploration to elucidate potential predictive factors. *Objective:* This cross-sectional study investigated the relationship between SBI and metabolic abnormalities prevalent in CKD stages 3-5 (non-dialytic) patients. *Methods:* Conducted at the Department of Nephrology, Dhaka Medical College Hospital, Dhaka, from September 2018 to March 2020, the study enrolled 115 participants. Group I comprised 85 CKD stage 3-5 (non-dialytic) patients without neurological symptoms, while Group II comprised 30 healthy controls. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Diseases equation. Magnetic resonance imaging (MRI) was performed on all subjects. Statistical analysis utilized SPSS-26. *Results:* The rate of Silent Brain Infarction is 52.9% in CKD patients. SBI was found in 45(52.9%) patients in group I and 4(13.3%) in group II. The differences were statistically significant (p<0.05). Glomerulonephritis (45.9%) was the leading cause of CKD among the study patients. Most of the patients with Hypertensive Nephrosclerosis (76.9%) had SBI, which indirectly showed its strong association. As the CKD stages progressed, the SBI rate also increased (stage-3:8.9%; stage-4:35.6%; stage-5ND:55.6%). In a multivariate logistic regression analysis, CKD had an independent relationship with SBI along with serum phosphate level and serum parathyroid hormone level (CKD had Odds ratio (OR)=1.847 (95.0% CI 0.064 to 53.319), serum PO4 had OR=0.958 (95.0% CI 0.885 to 1.038) and serum PTH had OR=0.996 (95.0% CI 0.993 to 1.000). Spearman rank correlation coefficient test showed a positive correlation between the occurrence of SBI and serum PO4 level (r=0.416; p=0.001) and serum PTH level (r= 0.405; p=0.001) separately. *Conclusions:* The high prevalence of SBI in CKD stage 3-5 (non-dialytic) patients underscores its clinical significance. Serum phosphate and parathyroid hormone levels positively correlate with SBI occurrence, highlighting their potential as predictive markers. Understanding these associations can inform risk stratification and guide targeted interventions in CKD management.

Keywords: Chronic Kidney Disease, Glomerular Filtration Rate, Hypertension, Magnetic Resonance Imaging, Silent Brain Infarction.

INTRODUCTION

Chronic kidney disease (CKD) represents a significant global health burden, with its prevalence steadily rising over the past decades [1]. Alongside its well-established cardiovascular complications, CKD has increasingly been associated with neurological morbidity and mortality, notably through the occurrence of silent brain infarction (SBI). While traditionally overlooked, the presence of SBI in CKD patients signifies underlying vascular pathology and imposes additional risks, including symptomatic stroke, cognitive decline, and mortality [2]. This paper aims to comprehensively review the pathophysiology of SBI in CKD, its clinical implications, and potential management strategies.

CKD patients often exhibit a constellation of biochemical abnormalities that contribute to the pathogenesis of SBI. Proteinuria, a hallmark of CKD, leads to systemic endothelial dysfunction, promoting gradual endothelial damage and leakage of serum proteins into the brain interstitial space, thus fostering perivascular changes conducive to SBI [3]. Furthermore, albuminuria in CKD patients has been associated with the production of uremic toxins, such as guanidine compounds, which exert direct neurotoxic effects and contribute to cortical thinning, further predisposing to SBI [4]. Anemia, prevalent in CKD, exacerbates cerebral hypoxia, leading to reversible focal deficits and potentially triggering cerebral infarctions, particularly in the context of severe atherosclerotic disease [5]. The compensatory increase in cerebral blood flow in anemic patients results in endothelial vessel damage and thrombus formation, thereby amplifying the risk of SBI [6].

Hyperphosphatemia and hyperparathyroidism are common metabolic abnormalities in CKD and affect cerebral vasculature and calcium metabolism. Elevated serum phosphate levels have been associated with vascular calcification and increased risk of all-cause mortality, including ischemic stroke, in CKD patients [7]. Hyperparathyroidism contributes to vascular stiffness, endothelial dysfunction, and cardiac remodeling, ultimately promoting cerebral infarction through increased blood pressure and vascular fibrosis [8]. Fibrinogen, a key player in hemostasis, has been implicated in atherosclerosis and ischemic stroke, with elevated levels correlating with increased stroke risk [9,10]. In CKD, dysregulation of fibrinogen further exacerbates the prothrombotic milieu, predisposing patients to SBI.

SBI serves as a harbinger of adverse neurological outcomes in CKD patients. Its presence predicts a higher risk of symptomatic stroke, cognitive impairment, and mortality, thus necessitating early detection and targeted intervention. Moreover, the coexistence of SBI with CKD exacerbates functional outcomes post-stroke, underscoring the need for integrated management strategies to mitigate its impact. The shared pathophysiological mechanisms between CKD and SBI underscore the importance of holistic management approaches targeting renal and neurological sequelae. Strategies aimed at mitigating proteinuria, correcting anemia, and optimizing mineral metabolism may attenuate CKD progression and mitigate the risk of SBI and its adverse consequences [11].

Early identification of SBI in CKD patients warrants comprehensive neurological assessment, including neuroimaging studies such as magnetic resonance imaging (MRI) to detect subtle cerebral lesions. Furthermore, aggressive management of modifiable risk factors, including hypertension, diabetes mellitus, and dyslipidemia, is paramount in mitigating the risk of SBI and its complications. Interventions targeting CKD-specific metabolic abnormalities, such as proteinuria and mineral dysregulation, hold promise in attenuating SBI progression. Pharmacological agents targeting endothelial dysfunction, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), have shown efficacy in reducing proteinuria and ameliorating vascular pathology, thereby potentially reducing the risk of SBI in CKD patients [12]. Additionally, optimizing anemia management through erythropoiesis-stimulating agents (ESAs) and iron supplementation may improve cerebral oxygenation and mitigate the risk of SBI in CKD patients. Calcium and phosphate-lowering therapies, including phosphate binders and calcimimetics, may attenuate vascular calcification and reduce the risk of SBI associated with hyperphosphatemia and hyperparathyroidism.

Silent brain infarction represents a significant yet often overlooked co-morbidity in CKD patients, contributing to adverse neurological outcomes and mortality. Understanding the shared pathophysiological mechanisms between CKD and SBI is paramount in guiding integrated management strategies to mitigate its impact. Comprehensive neurological assessment, aggressive management of modifiable risk factors, and targeted interventions addressing CKD-specific metabolic abnormalities are essential in reducing the burden of SBI and improving outcomes in CKD patients. Further research is warranted to elucidate optimal management strategies and improve clinical outcomes in this high-risk population.

OBJECTIVES

General Objectives

- To find out the relationship between SBI and the metabolic abnormality found in CKD patients stage 3-5 (non-dialytic).

Specific Objectives

- To find out the rate of SBI in CKD stage 3-5 (non-dialytic) patients.
- To estimate the metabolic abnormalities in CKD stage 3-5 (non-dialytic) patients having SBI (anemia, hypoalbuminaemia, hypocalcaemia, hyperphosphataemia, hyperparathyroidism, hyperfibrinogenemia, dyslipidaemia).
- To find the individual relationship between SBI and each metabolic abnormality component found in CKD stage 3-5 (non-dialytic) patients.

MATERIALS AND METHODS

Study Design

A cross-sectional study conducted at Dhaka Medical College Hospital from September 2018 to March 2020 focused on chronic kidney disease (CKD) patients in stages 3-5, devoid of stroke symptoms. Employing purposive sampling, the study aimed to elucidate the prevalence of silent brain infarction (SBI) and its association with metabolic abnormalities. This design allowed for a snapshot evaluation of SBI occurrence in CKD patients, providing valuable insights into the potential neurological implications of the disease.

Inclusion Criteria

- CKD patients who are staged 3-5 non-dialytic as per GFR criteria (MDRD equation)

Exclusion Criteria

- CKD patients (stage 3-5 non-dialytic) with any features of neurological involvement suggesting stroke, such as hemiplagia, hemiparesis, facial asymmetry, visual abnormality, vertigo, abnormal movement, cognitive dysfunction, and altered level of consciousness.

Data Collection

Structured questionnaires were utilized to systematically collect participants' demographic information, medical history, and examination findings. Informed consent was obtained from all subjects, ensuring ethical considerations were met. The comprehensive data collection process facilitated a thorough understanding of the study population and enabled the identification of potential risk factors for silent brain infarction. Rigorous adherence to standardized protocols during data collection minimized biases and ensured the reliability of the study findings.

Data Analysis

Data analysis was conducted using IBM SPSS Statistics version 26, a robust statistical software package. Descriptive statistics were employed to summarize the characteristics of the study population, presenting quantitative variables as means ± standard deviations and qualitative variables as percentages or frequency distributions. The chi-square test was utilized to explore associations between categorical variables, while multivariate logistic regression analysis investigated factors influencing the presence of silent brain infarction. A significance level of $p < 0.05$ was applied to all statistical tests, ensuring the validity of the study results and supporting evidence-based conclusions. Different variables like eGFR, BP, Hb%, serum creatinine, S. albumin, S. Ca, PO4, PTH, S. fibrinogen level, T. cholesterol and TG and their association with SBI were analyzed through multivariate logistic regression analysis. A level of $P< 0.05$ was considered statistically significant.

Ethical Consideration

Ethical approval was paramount throughout the study conducted at the Department of Nephrology, Dhaka Medical College Hospital. Informed consent was obtained from all participants, ensuring voluntary participation and respect for individual autonomy. The institutional ethics committee approved the study protocol, adhering to established guidelines for human research. Confidentiality of participants' data was maintained at all stages of the study, safeguarding their privacy and anonymity. Additionally, participants were informed of potential risks and benefits associated with the study, promoting transparency and accountability in research conduct.

RESULTS

Table 1: Distribution of the study subjects by age (N=115)

Age (in years)	Group I (n=85)		Group II (n=30)		P value
	n	%	n	%	
<20	2	2.35	1	3.33	
20-29	6	7.06	2	6.67	
30-39	15	17.65	3	10.00	

Age (in years)	Group I (n=85)		Group II (n=30)		P value
	n	%	n	%	
40-49	23	27.06	8	26.67	
50-59	19	22.35	9	30.00	
60-69	15	17.65	4	13.33	
≥70	5	5.88	3	10.00	
Mean±SD	47.24±13.65		49.4±15.54		0.474
Range (min-max)	17-79		14-80		

Table I shows the distribution of the study patients by age. It was observed that 23(27.06%) patients belonged to age 40-49 years in group I and 8(26.67%) in group II. The mean age was 47.24±13.65 years in group I and 49.4±15.54 years in group II. The differences were statistically not significant (p>0.05) between two groups.

Table 2: Distribution of the study subjects by silent brain infarction (N=115)

Silent brain infarction	Group I		Group II		OR (95%CI)	P value
	n	%	n	%		
Present	45	52.9	4	13.3	7.13(2.16-27.20)	0.001
Absent	40	47.1	26	86.7		

The study patients by silent brain infarction. It was observed that more than half (52.9%) of patients had silent brain infarction in group I and 4(13.3%) in group II. Silent brain infarction had 7.13 (95.0% CI 2.16 to 27.20). The differences was statistically significant (p<0.05) between two groups.
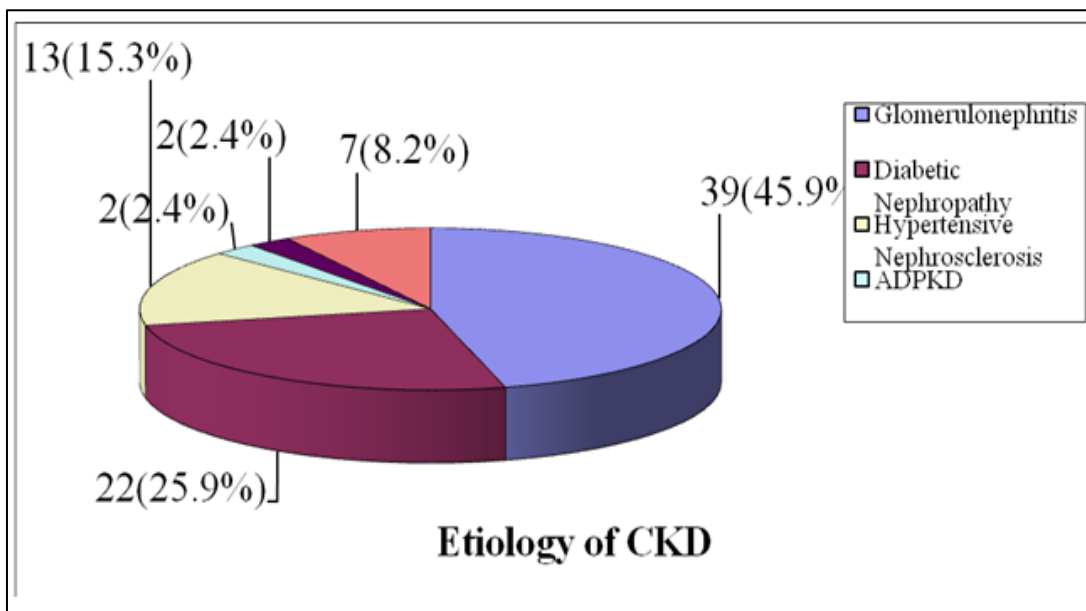

Figure 1: Pie chart showing the distribution of the study patients by Etiology of CKD

Pie chart shows the distribution of the study patients by etiology of CKD; it was observed that almost half (45.9%) patients had glomerulonephritis, followed by 22(25.9%) diabetic nephropathy, 13(15.3%) hypertensive nephrosclerosis, 2(2.4%) ADPKD, 2(2.4%) obstructive nephropathy and 7(8.2%) unknowns.

Table 3: Distribution of the study patients by co-morbidity

Co-morbidity	SBI (n1=45)		Without SBI (n2=40)		P value
	n	%	n	%	
H/O DM	17	37.8	13	32.5	0.611
H/O HTN	37	82.2	30	75.0	0.416
H/O DM and HTN	13	28.9	7	17.5	0.216

Medical records will be distributed to the study patients. It was observed that more than one-third (37.8%) of patients had DM in SBI and 13(32.5%) without SBI. Most (82.2%) patients had H/O HTN in SBI and 30(75.0%) without SBI. More than one-fourth (28.9%) of patients had H/O DM and HTN in SBI, and 7(17.5%) in without SBI. The differences were statistically insignificant (p>0.05) between the two groups.
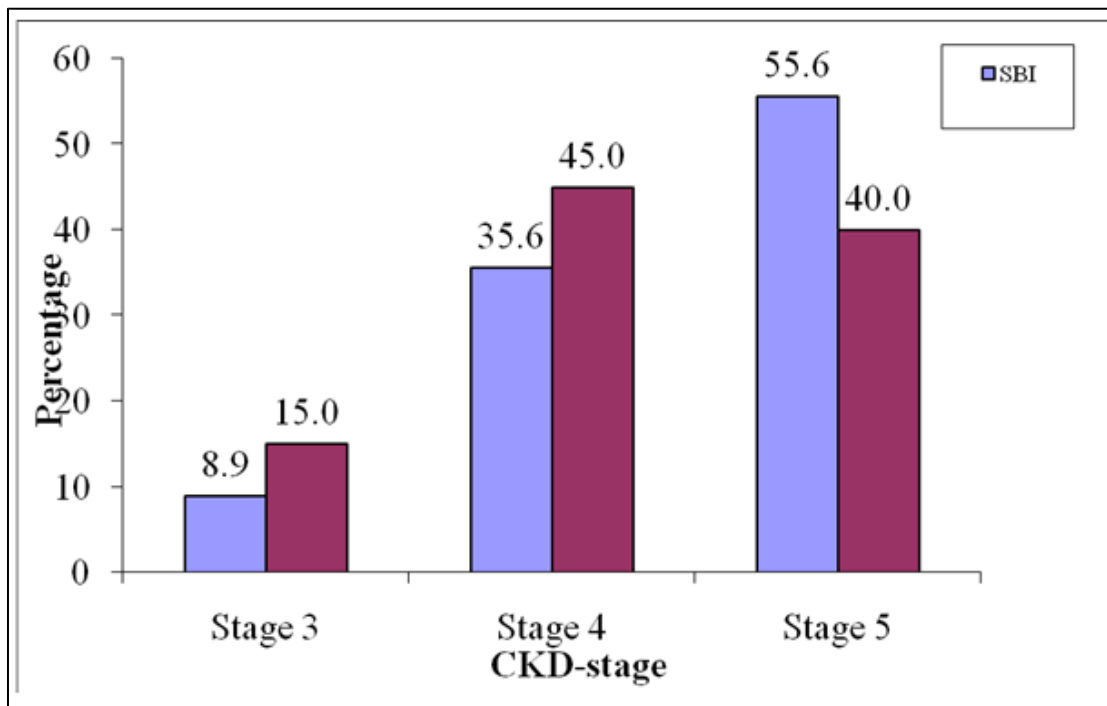

Figure 2: Bar diagram showing the distribution of the study patient by CKD stage (with SBI status)

Table 4: Distribution of the study patients by etiology of CKD with SBI status (Group I)

Etiology of CKD	SBI		Without SBI		P value
	n	%	n	%	
Glomerulonephritis (n=39)	15	38.5	24	61.5	0.095
Diabetic Nephropathy (n=22)	14	63.6	8	36.4	
Hypertensive Nephrosclerosis (n=13)	10	76.9	3	23.1	
ADPKD (n=2)	2	100.0	0	0.0	
Obstructive Nephropathy (n=2)	1	50.0	1	50.0	
Unknown (n=7)	3	42.9	4	57.1	

The distribution of the study patients by etiology of CKD by SBI status. It was observed that more than three-fourths (76.9%) of patients had hypertensive nephrosclerosis in SBI and 3(23.1%) without SBI. The differences were statistically insignificant (p>0.05) between the two groups.
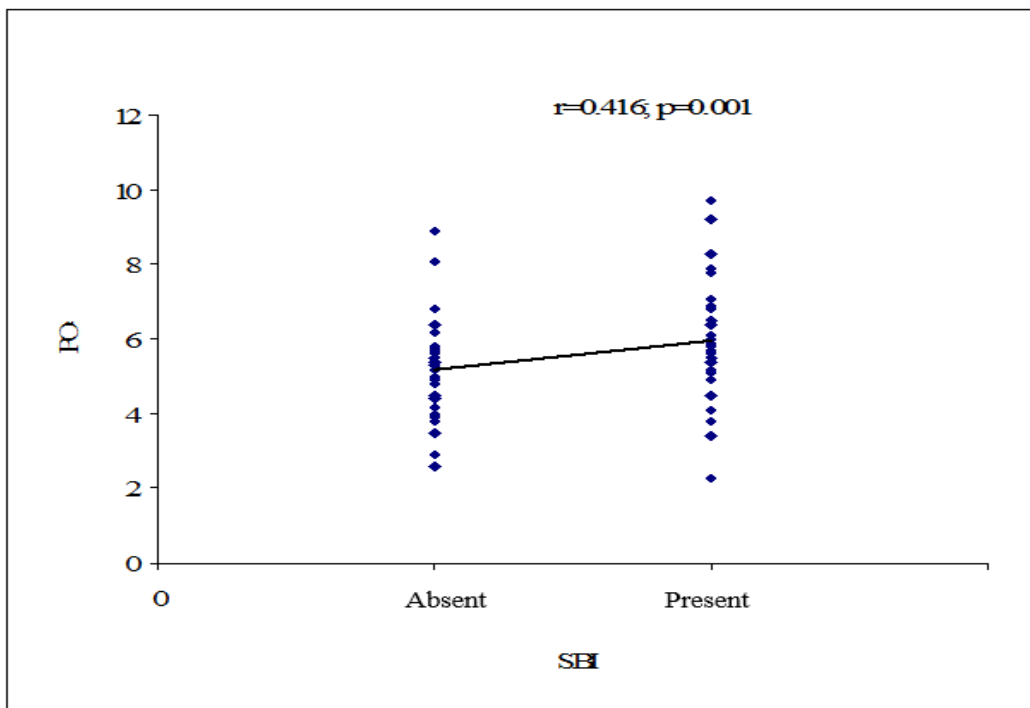
Figure 3: Scatter diagram showing positive significant Spearman rank correlation (r=0.416; p=0.001) between SBI with PO4
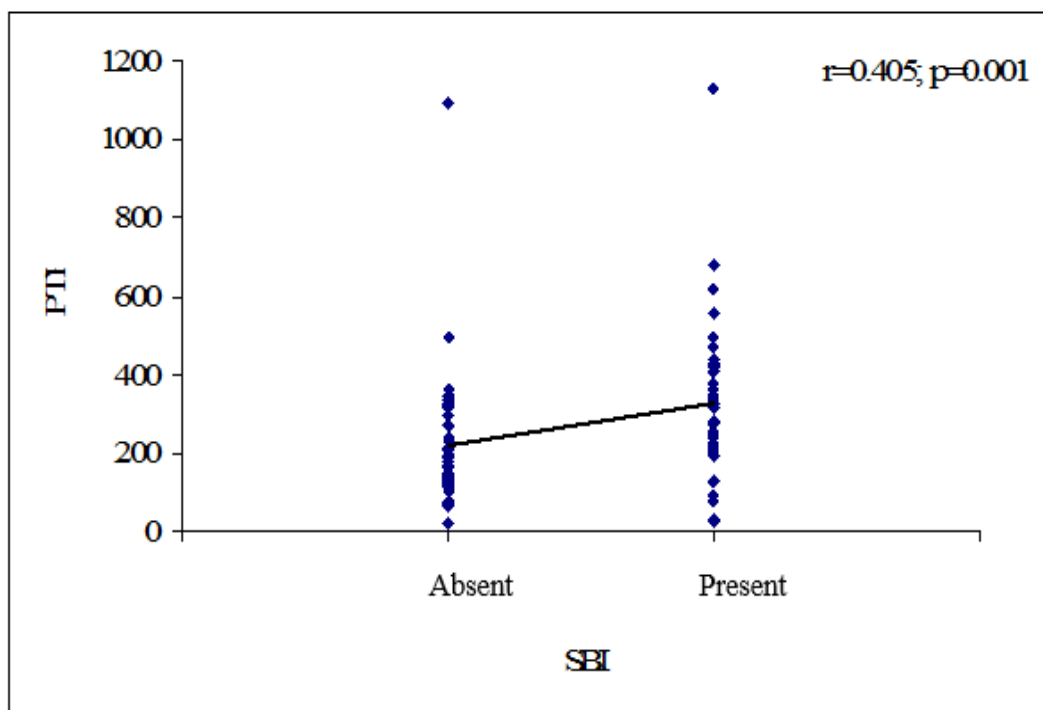

Figure 4: Scatter diagram showing positive significant Spearman rank correlation (r=0.405; p=0.001) between SBI with PTH

DISCUSSION

In the multivariate logistic regression analysis, SBI was significantly associated with CKD, with an odds ratio of 1.847 and a 95.0% confidence interval of 0.064 to 53.319. This finding supported previous research suggesting an independent association between SBI and CKD, possibly due to shared vascular pathophysiology between the kidneys and the brain [13]. Moreover, the analysis revealed significant associations between SBI and serum phosphate levels (OR 0.958, 95.0% CI 0.885 to 1.038) and serum PTH levels (OR 0.996, 95.0% CI

0.993 to 1.000). The Spearman rank correlation further supported these associations, indicating positive correlations between SBI and serum phosphate and PTH levels. These findings contradicted some previous studies but were consistent with others, highlighting the need for further investigation into the role of these metabolic factors in SBI development among CKD patients. The study discussed potential mechanisms underlying these associations, such as inflammation, enhanced coagulability, anemia, calcium-phosphate abnormalities, and proteinuria, commonly observed in CKD patients. However, the exact mechanisms linking these factors to SBI remain unclear and require additional research for clarification.

Additionally, the study provided insights into the prognostic implications of elevated serum phosphate levels, showing an increased risk of mortality associated with higher phosphate concentrations in patients with CKD. These findings underscored the importance of monitoring and managing metabolic abnormalities in CKD patients to improve outcomes and reduce the risk of complications such as SBI. In the multivariate logistic regression analysis, SBI was significantly associated with CKD, with an odds ratio of 1.847 and a 95.0% confidence interval of 0.064 to 53.319 [14,15]. This finding supported previous research suggesting an independent association between SBI and CKD, possibly due to shared vascular pathophysiology between the kidneys and the brain. Moreover, the analysis revealed significant associations between SBI and serum phosphate levels (OR 0.958, 95.0% CI 0.885 to 1.038) and serum PTH levels (OR 0.996, 95.0% CI 0.993 to 1.000. The Spearman rank correlation further supported these associations, indicating positive correlations between SBI and serum phosphate and PTH levels [16]. These findings contradicted some previous studies but were consistent with others, highlighting the need for further investigation into the role of these metabolic factors in SBI development among CKD patients.

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outcomes and reduce the risk of complications such as SBI.

In our study, silent brain infarction (SBI) was 52.9% in CKD patients (stage 3-5, non-dialytic), whereas only 13.3% of healthy controls exhibited SBI. This indicates a substantial difference in SBI prevalence between CKD patients and non-CKD individuals. Moreover, SBI was significantly associated with CKD, with a 7.13-fold increased risk compared to healthy controls (p < 0.05, 95% CI: 2.16 to 27.20). Additionally, when stratified by CKD stage, our findings revealed a progressive increase in the prevalence of SBI with the advancing CKD stage. Specifically, in CKD stage-5 (eGFR <15), 55.6% of patients had SBI, while in CKD stage-4 (eGFR 15-30) and stage-3 (eGFR 30-60), the prevalence of SBI was 35.6% and 8.9%, respectively [18]. These results are consistent with previous research, which has demonstrated a positive correlation between CKD severity and SBI prevalence, with higher CKD stages associated with a greater likelihood of SBI occurrence. These findings highlight the importance of regular screening for cerebrovascular complications, particularly in advanced CKD stages, to facilitate early detection and appropriate management strategies [19]. Overall, the study contributed valuable information to understanding the relationship between SBI and metabolic abnormalities in CKD patients, highlighting the need for further research to elucidate underlying mechanisms and identify potential therapeutic targets for intervention.

CONCLUSIONS

Our study highlights a high prevalence of silent brain infarction (SBI) in CKD stage 3-5 (non-dialytic) patients, with serum phosphate and parathyroid hormone levels showing positive correlations with SBI occurrence. These findings underscore the importance of monitoring and managing metabolic abnormalities in CKD patients to prevent cerebrovascular complications. Further research is warranted to elucidate underlying mechanisms and optimize therapeutic strategies for improving outcomes in this high-risk population.

RECOMMENDATIONS

Serum phosphate and parathyroid levels should be kept within normal reference levels in CKD (stage 3-5 ND) patients to prevent SBI.

In the future, a large-scale study can be undertaken with a large sample size covering different areas of the country.

ACKNOWLEDGMENT

Abbreviations

SBI – Silent Brain Infarction
CKD - Chronic Kidney Disease
ND - Non-dialytic
GN - Glomerulonephritis
HTN - Hypertension
CI - Confidence Interval
MRI - Magnetic Resonance Imaging
CS - Community Sample
WML - White Matter Lesion
IDA - Iron Deficiency Anemia

Conflict of Interest: None declared.

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