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The Prevalence and Severity of Headaches in Hemodialysis Children: A Comparative Study

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ABSTRACT

Background: One of the symptoms of chronic kidney disease (CKD), especially in individuals receiving regular hemodialysis (HD), is headache.

Objective: This study aims to describe the prevalence, characteristics, and consequences of headaches on children with CKD's quality of life as assessed by the Headache Impact Test-6 (HIT-6) score.

Methods: The CKD group (n = 50) and the HD group (n = 50) were included in this cross-sectional comparative analysis. The prevalence, characteristics, frequency, and severity of headaches were compared between the two patient groups.

Results: The prevalence and frequency of headache were significantly higher in the HD group than in the CKD group with p-values: <0.001, 0.003 respectively. Patients with headache had significantly lower GFR and serum sodium (p-values: 0.002, 0.006) but higher serum phosphate and PTH (p-values: 0.035, 0.005) than those without headache. In HD patients, The HIT-6 score was found to have a statistically significant positive correlation with serum magnesium (p = 0.012, r = 0.412) and a statistically significant negative correlation with serum sodium (p = 0.006, r: -0.474).

Conclusions: Headaches are more prevalent and more frequent in CKD children on HD than in those on conservative treatment. In HD patients, lower serum sodium and higher serum magnesium increase the headache severity based on the HIT-6 score.

Keywords: Chronic Kidney Disease, Hemodialysis, Headache.

INTRODUCTION

In children, the frequency of chronic kidney disease (CKD) has been rising globally [(1)], and it affects their quality of life because of comorbid conditions that are related to it and the requirement for kidney replacement therapy (KRT), such as hemodialysis (HD) or peritoneal dialysis (PD) [(2)].

One of the symptoms associated with CKD patients, especially those receiving regular hemodialysis, is headache, as a result of abnormal hemodynamic parameters such as blood pressure and abnormal levels of electrolytes such as urea, sodium, and magnesium [(3)].

Headaches have a significant impact on children's quality of life. The Headache Impact Test-6 (HIT-6) score is used to measure how much a headache impacts an individual's quality of life; a higher score means that the headache has a greater effect on the daily life of the respondent. [(4)]

Several studies have described headache in CKD and hemodialysis patients in adults [(5, 6)], although the published data in pediatric patients is limited [(7)].

In relation to the HIT-6 score, this study is the first to describe headache in pediatric CKD patients, whether on HD or not.

This study aims to describe the prevalence, frequency, and characteristics of headaches in children with CKD who are receiving HD or conservative therapies, as well as how these headaches affect their quality of life as measured by the HIT-6 score.

PATIENTS AND METHODS

One hundred patients enrolled in this cross-sectional study. The CKD group consisted of fifty patients with CKD (stages 3, 4 and 5) who received conservative treatment and followed up at a nephrology clinic at a tertiary care Cairo University Children's Hospital, and fifty patients (HD group) with CKD5D who received regular hemodialysis by conventional low flux machines with bicarbonate-based dialysate three times per week at the Dialysis Unit of the Centre of Pediatric Nephrology and Transplantation, Children's Hospital, Cairo University, for at least six months.

The study included children ages between 10 and 18 years old (as they can describe the symptoms). Patients with neurological or cognitive abnormalities, as well as those with dental, otolaryngological, or ophthalmological issues, were excluded. [(8)]

Ethical Consideration:

The work was approved by the Ethical Committee of Faculty of Medicine, Cairo University number MS-164-2019. Informed consent was obtained and documented from the legal guardian/parents of the participants.

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The Declaration of Helsinki 1967's principles were followed in all of the study's processes.
The following was done:

Age, sex, primary renal disease, onset of renal impairment, onset and duration of hemodialysis, onset of headache and its relation to hemodialysis in hemodialysis patients, location of headache (frontal, frontal temporal, temporal, parietal), headache character, related symptoms (vomiting, photophobia, phonophobia), duration of each attack, and frequency of the attacks per month. The diagnosis of headache was done according to the International Classification of Headache Disorders (ICHD-3) beta version criteria [(9)] in the pediatric neurology clinic at our hospital. The HIT-6 score was used to evaluate the severity of headaches [(10)].

Complete physical examination and vital signs, including blood pressure. Investigations: Complete blood count, serum ferritin, kidney function tests (urea, creatinine), serum (calcium, phosphorus, magnesium, alkaline phosphatase), blood gases, and parathyroid hormone.

Statistical Analysis

SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) and Med Calc 13 for Windows were used to gather, tabulate, and statistically analyze all of the data (Med Calc Software bvba, Ostend, Belgium). The data's normal distribution was checked using the Shapiro Wilk test. We characterized the qualitative data using frequencies and relative percentages.

According to the results of the Chi square test, the difference between qualitative variables was estimated. For the purpose of representing quantitative data, mean and standard deviation (SD). For parametric and non-parametric variables, respectively, the independent T test and the Mann Whitney test were employed to compare numerical variables between two groups. Pearson's correlation coefficients were used for numerical association. All statistical comparisons were two-tailed. A significant difference is one with a P-value of 0.05 or less and a highly significant difference is one with a P-value of 0.001.

RESULTS

A total of 100 children with CKD were included in this cross-sectional comparative study, which included two groups: the CKD group (n = 50) and the HD group (n = 50) (Figure 1).

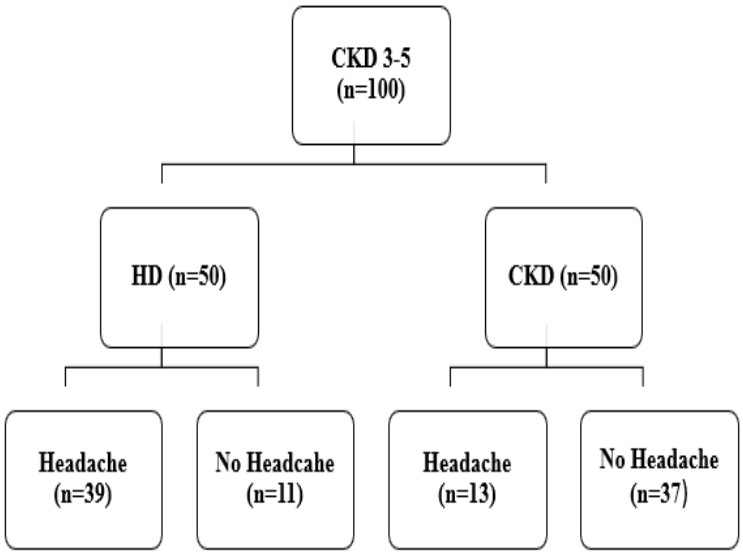

Figure 1: Flow chart illustrates the study population

The descriptive data of the study group:

The average age of the study group was 11.35 ±3.46 years and it was significantly higher in the HD group than CKD group. Males (n = 51) and females (n = 49) were almost equally distributed. The most common primary renal disease among the study group was congenital anomalies of the kidney and urinary tract (CAKUT) at 28% (n = 28), followed by focal segmental glomerulosclerosis (FSGS) at 18% (n = 18) (Table 1).

Comparison between HD group and CKD group:

In the HD group, the disease duration was significantly longer than in the CKD group. In comparison to the CKD group, the HD group's anemia was noticeably worse and the GFR, serum sodium, and serum calcium were all significantly lower in the HD group. While serum ferritin and serum PTH were significantly greater in the HD group than in the CKD group (Table 1).

Table (1): Demographic, clinical and laboratory data of the study group

Variable		***HD*** *(n=50)*	***CKD*** *(n=50)*	***t / Chi² test***	***p-value***
Demographic data					
Age *(years), Mean ± SD*		13.87 ± 2.83	11.13 ± 4.76	**3.49***	**0.001**
Sex	*Male*	27 (54%)	24 (48%)	0.361	0.548
	Female	23 (46%)	26 (52%)		
Weight *(Kg) Mean ± SD*		47 ± 9.05	43.38 ± 15.52	1.42*	0.157
Height *(cm) Mean ± SD*		151.64 ± 9.21	143.88 ± 13.38	**3.38**	**0.001**
Clinical data					
The primary renal disease					
CAKUT		13 (26%)	15 (30%)	6.46	0.595
Polycystic kidney		4 (8%)	5 (10%)		
Chronic interstitial nephritis		2 (4%)	5 (10%)		
FSGS		12 (24%)	6 (12%)		
Nephrolithiasis		4 (8%)	4 (8%)		
Thrombotic microangiopathy (hemolytic uremic syndrome)		3(6%)	5 (10%)		
lupus nephritis		3(6%)	5 (10%)		
Nephrocalcinosis		2 (4%)	1 (2%)		
Unknown		7 (14%)	3 (6%)		
Duration of disease *(years) Mean ± SD*		6.86 ± 3.17	9.06 ± 4.49	**2.83***	**0.006**
HD duration *(month), Mean ± SD*		12.5 ± 5.98	--		
Laboratory data					
Hemoglobin (g/dl), *Mean ±SD*		10.31 ± 1.13	11.88 ± 1.69	**5.46**	**<0.001**
TLC (x10³/L), *Mean ±SD*		8.72 ± 1.83	7.86 ± 1.99	**1.07***	**0.287**
PLT (x10³/L), *Mean ±SD*		319.95 ± 9.26	351.88 ± 8.95	**1.74***	**0.085**
Creatinine (mg/dl) *Mean ±SD*		7.68 ± 1.34	3.85 ± 0.24	**10.23***	**<0.001**
Urea (mg/dl) *Mean ±SD*		138.24 ± 9.18	82.33 ± 4.75	**6.91***	**<0.001**
GFR (mL/min/1.73m²) *Mean ±SD*		11.87 ± 2.72	42.87 ± 2.54	**10.5***	**<0.001**
Ferritin (ng/ml) *Mean ±SD*		372.14 ± 23.2	78.52 ± 9.54	**7.91***	**<0.001**
Sodium (mEq/L) *Mean ±SD*		136.61 ± 5.27	138.74 ± 2.56	**2.57**	**0.012**
Potassium (mEq/L) *Mean ±SD*		4.72 ± 0.643	4.78 ± 0.684	**0.452**	**0.652**
Calcium (mg/dl), *Mean ±SD*		8.68 ± 1.34	9.38 ± 0.724	**3.25**	**0.002**
Phosphate (mg/dl), *Mean ±SD*		5.24 ± 1.08	4.93 ± 0.754	**1.66**	**0.099**
Magnesium (mg/dl), *Mean ±SD*		2.52 ± 0.716	2.29 ± 0.403	**1.98***	**0.051**
PTH (ng/L) *Mean ±SD*		423.7 ± 23.4	187.38 ± 13.9	**4.67***	**<0.001**
Bicarbonate (nmol/L) *Mean ±SD*		23.4 ± 2.58	24.1 ± 2.33	**1.42**	**0.158**

CAKUT: Congenital anomalies of the kidney and urinary tract, CKD: Chronic Kidney disease, FSGS: Focal segmental glomerulosclerosis, GFR: Glomerular filtration rate, HD: Hemodialysis, PLT: Platelets count, PTH: Parathormone, SD: Standard deviation, TLC: Total leucocytic count. *: Mann-Whitney test

Headache characteristics of the study group:

Headache frequency was significantly higher in HD. The HIT-6 score revealed that the CKD group has more severe headaches than the HD group but did not reach statistical significance as shown in table 2. A higher score implies that the respondent's daily life has been more significantly impacted by headaches.

Table (2): Headache characteristics and severity of the study group

Variable		***Patients with headache among HD group*** *(n=39)*	***Patients with headache among CKD group*** *(n=13)*	***t / Chi^2 test***	***p-value***
Age at headache onset *(years)* *Mean ± SD*		10.46 ± 4.22	8.97 ± 3.83	1.13*	0.265
Type	*Migraine*	26 (52%)	8 (16%)	0.113	0.736
	Tension	13 (26%)	5 (10%)		
Headache frequency *(per months)* *Mean ± SD*		5.76 ± 4.31	1.63 ± 1.17	**3.21***	**0.003**
Attack duration *(hours)* *Mean ± SD*		9.35 ± 9.58	14.2 ± 19.31	0.962*	0.336
HIT-6 score (Mean ± SD)		56 ± 7.38	58 ± 7.19	0.85	0.398
Impact grades					
Little-to-no impact HIT-6 score (≤ 49)		2 (5.1%)	1 (7.7%)	0.118	0.731
Moderate impact HIT-6 score (50-55)		10 (25.6%)	3 (23%)	0.034	0.853
Substantial impact HIT-6 score (56-59)		18 (46.2%)	5 (38.4%)	0.234	0.629
Severe impact HIT-6 score (≥60)		9 (23.1%)	4 (30.7%)	0.307	0.579

CKD: Chronic Kidney disease, HD: Hemodialysis, HIT-6 score: Headache Impact Test-6.*: Mann-Whitney test

Patients who had headaches were significantly older than those who did not. Additionally, their systolic and diastolic blood pressure were significantly higher. The proportion of HD patients in patients who had headache was significantly higher than those who did not. Patients with headache had significantly lower GFR and serum sodium, but higher serum phosphate and PTH (Table 3).

Table (3): Comparison between patients with and without headaches regarding (Demographic, clinical and laboratory data)

Variable		*Patients with headache (n=52)*	*Patients without headache (n=48)*	*t / Chi² test*	*P-value*
Demographic data					
***Age** (years), Mean ± SD*		13.67 ± 1.96	11.25 ± 3.19	**4.61***	**<0.001**
Sex	*Male*	31 (59.6%)	20 (41.7%)	3.22	0.073
	Female	21 (40.4%)	28 (58.3%)		
Clinical data					
***Duration of disease** (years) Mean ± SD*		8.54 ± 2.37	7.94 ± 4.47	0.848*	0.399
***SBP** (mmHg), Mean ±SD*		129.13 ± 12.44	123.74 ± 11.48	**2.25**	**0.027**
***DBP** (mmHg), Mean ±SD*		83.22 ± 8.55	75.39 ± 9.42	**4.36**	**<0.001**
Cardiac diseases		15 (28.8%)	9 (16.7%)	1.39	0.238
Hemodialysis patients		39 (75%)	11 (22.9%)	**27.1**	**<0.001**
Laboratory data					
***Creatinine** (mg/dl), Mean ±SD*		4.23 ± 9.51	3.11 ± 3.04	0.779*	0.437
***GFR** (mL/min/1.73m^2), Mean ±SD*		20.41 ± 24.3	39.71 ± 36.21	**3.15***	**0.002**
***Sodium** (mEq/L), Mean ±SD*		135.64 ± 5.12	137.82 ± 1.81	**2.79**	**0.006**
***Potassium** (mEq/L), Mean ±SD*		4.81 ± 0.774	4.73 ± 0.652	0.557	0.579
***Calcium** (mg/dl), Mean ±SD*		9.26 ± 1.21	9.51 ± 0.568	1.31	0.195
***Phosphate** (mg/dl), Mean ±SD*		5.21 ± 1.23	4.76 ± 0.812	**2.14**	**0.035**
***Magnesium** (mg/dl), Mean ±SD*		2.37 ± 0.411	2.33 ± 0.452	0.463	0.644
***PTH** (ng/L), Mean ±SD*		341.7 ± 317.5	190.51 ± 182.5	**2.89***	**0.005**
***Bicarbonate** (nmol/L), Mean ±SD*		23.62 ± 3.42	23.15 ± 2.67	0.762	0.448

DBP: Diastolic blood Pressure, GFR: Glomerular filtration rate, PTH: Parathormone, SBP: Systolic blood pressure.
*: Mann-Whitney test

Headache in CKD patients on conservative treatment was mostly generalized and mostly associated with photophobia or phonophobia, whereas headache in HD patients was mostly bifrontal and also associated with photophobia as shown in table 4. The type of headache in CKD patients was migraine in 69% of the patients (n=9/13) and tension headache in 31% (n=4/13), while in HD group migraine presented in 66% of cases (n=26/39) and tension headache in 34% of case (n=13/39). It was found that the headache occurs mostly after dialysis in 48% (n=19/39) of HD patients or during dialysis in 35% (n=14/39) of HD patients.

Table (4): Headache characters in CKD and HD patients

Variable	***CKD** (n=13)*	***HD** (n=39)*
	N (%)	***N (%)***
Localization of headache		
Bifrontal	2 (15.3%)	16 (41%)
Vertex	1 (7.6%)	6 (15.4%)
Generalized	6 (46.1%)	10 (25.6%)
Bitemporal	3 (23%)	4 (10.3%)
Occipital	1 (7.6%)	3 (7.7%)
Comorbid symptoms of headache		
Phonophobia	8 (61.5%)	17 (43.6%)
Photophobia	11 (84.6%)	16 (41%)
Dizziness	7 (17.9%)	11 (28.2%)
Vomiting	8 (20.5%)	13 (33.3%)

CKD: Chronic Kidney Disease, HD: Hemodialysis.

The HIT-6 score was found to have a statistically significant negative correlation with serum sodium (p = 0.006, r: -0.474) figure 2 and a statistically significant positive correlation with serum magnesium (p = 0.012, r = 0.412) figure 3 and serum creatinine (p = 0.02, r = 0.391).

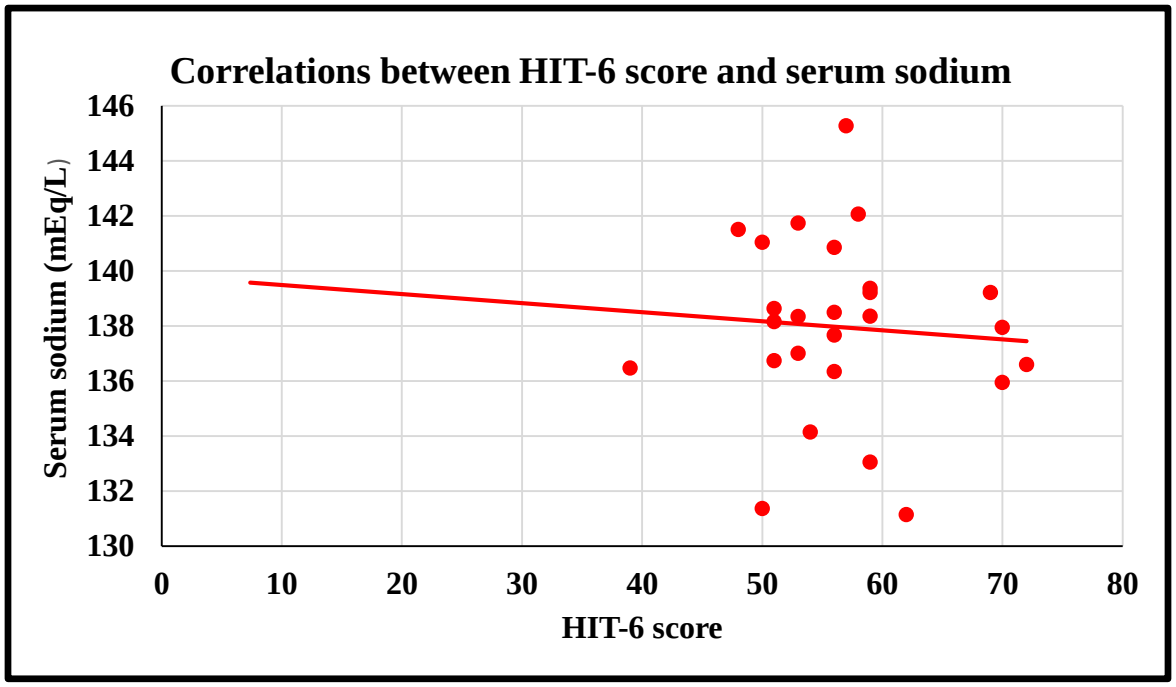

Figure 2: Correlations between HIT-6 score and serum sodium

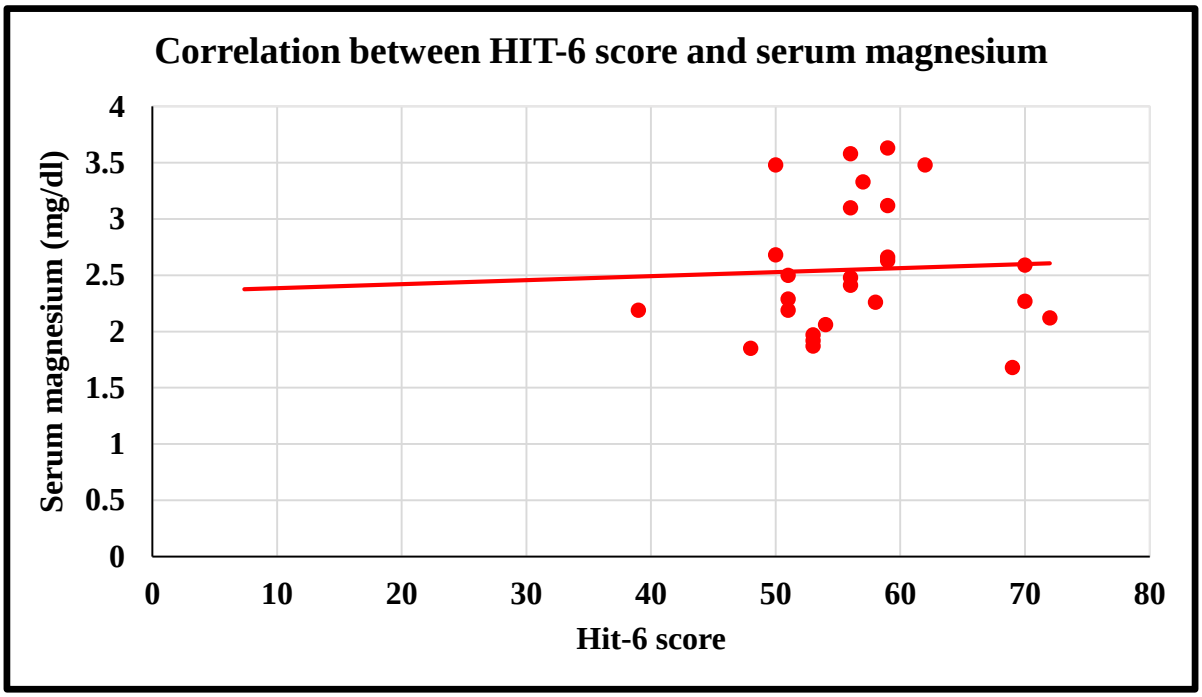

Figure 3: Correlations between HIT-6 score and serum magnesium

DISCUSSION

In this study, we noticed that headaches are more prevalent and more frequent in hemodialysis children when compared to CKD children who received conservative treatment. Headaches mainly occur after HD sessions. Dialysis headache occurs mainly due to fluctuations in the serum levels of urea, magnesium, sodium, and substance P during dialysis. Additionally, it is related to changes in arterial blood pressure, concentration differences between the blood and the brain, and water passing through the blood-brain barrier, causing some degree of cerebral edema [(11)].

With a p-value of 0.00001, patients with headaches have a greater proportion of HD patients than patients without headaches. We found that headache occurs mostly after dialysis in 48% (n=19/39) of HD patients or during dialysis in 35% (n=14/39) of HD patients **.**This is attributed to variations in serum electrolytes and blood pressure during dialysis in HD patients. This is consistent with several studies that show patients with HD experience headaches more frequently than those with CKD receiving conservative treatment whether in children [(7)] or adults [(12)].

In our HD Unit, all children were treated by bicarbonate dialysate. In a study done on adults, it showed that the headache was more severe and more frequent in patients treated with acetate-based dialysis when compared to those who used bicarbonate-based dialysis [(13)]. The HIT-6 score is used to evaluate how a headache impacts a patient's daily activities [(14)]. This is the first published paper that uses this score in pediatric CKD and HD patients. According to the HIT-6 score, the CKD group has more severe headaches than the HD group, but did not reach statistical significance. We have no clear explanation regarding this but it may be related to the prevalence of the type of headache in each group. As is well known, migraine is considered more severe than tension headache [(15)] and the migraine was more frequent in the CKD group than the HD group, with a prevalence of 69% (n=9/13) compared to 66% (n=26/39). Patients who had headaches were significantly older than those who did not. The older one can explain the symptoms more than the younger one. Additionally, their systolic and diastolic blood pressure were higher. This agrees with a study that showed hypertension in children is associated with an increased incidence of migraine when compared to those without hypertension [(16)]. This is also consistent with a study that found adult patients with headaches on dialysis have significantly higher systolic and diastolic blood pressure compared to the control group [(17)]. But this disagrees with a study on postmenopausal women that showed that increased systolic blood pressure reduces the prevalence of headache through modulation of baroreflex and the development of hypertension associated hypoalgesia [(18)].

In this work, it was found that patients with headache had significantly lower GFR and serum sodium, but higher serum phosphate and PTH. This agrees with a study done on CKD children with and without HD, which showed lower GFR more in children with headache [(7)].

One of the neurological side effects of hyponatremia in children is headache. Low serum sodium decreases serum osmolarity and leads to a secondary shift of water into the brain cells, leading to neurological symptoms including headache [(19)].

This agrees with a study done on adult patients that showed higher serum phosphate in patients with migraine than the control group with a p-value of p=0.016. This indicates that the higher serum phosphate could contribute to the pathophysiology of headaches [(20)].

Hyperparathyroidism is associated with headache due to associated hypercalcemia [(21)], but in this study, there was no significant different in serum calcium levels between headache- and headache-free patients.

In this article, we studied the correlations between the HIT-6 score, which showed how the patient's activities were affected by the headache, and various parameters were used to assess the severity of headache in HD patients.

HIT-6 score was found to have a statistically significant negative correlation with serum sodium and a statistically significant positive correlation with serum creatinine and magnesium. HIT-6 score and serum sodium had a significant negative correlation. More hyponatremia causes more brain cell edema, which makes headache more severe [(19)]. In this work, we observed that the HIT-6 score and serum magnesium had positive correlations. Although magnesium deficiency increases the risk of headache, in this work, between patients with and without headaches, there was no statistically significant difference in the levels of magnesium. Magnesium plays a significant role in enzyme activity and neuromuscular excitability with regulation of cerebrovascular dilatation. Additionally, oral magnesium is recommended to relieve headaches, particularly migraines when given early during aura stage [(22)].

One of the pathophysiology theories for migraine suggests that the meningeal blood vessels' vasodilation is what causes the pain, but vasoconstriction usually occurs in the early stage of migraine (aura) [(23)].

This disagrees with a study done on adult patients with migraine that showed the serum magnesium is lower in severe headaches in comparison with mild to moderate headaches ($p = 0.01$) [(24)]. Another study showed that adult patients with tension headaches or migraines, with or without aura, had significantly lower serum magnesium levels [(25)]. This could explain why increased magnesium levels induce more severe headaches because higher magnesium levels during the aura stage cause an amplification of vasodilatation.

The study's limitations were the need for a larger patient population. Additionally, several correlations between headache and other hemodialysis parameters such as dialysis adequacy, dialysis frequency, vascular access, and the type of dialysis machine required to be studied.

CONCLUSIONS

Headaches are more prevalent and more frequent in CKD children on HD than in those on conservative treatment. Systolic and diastolic blood pressure are higher in children with headaches. In HD patients, lower serum sodium and higher serum magnesium increase the severity of headache according to the HIT-6 score. We recommend proper control of blood pressure and serum electrolytes, particularly serum magnesium and sodium, in HD children to decrease the frequency and severity of headache in those children.

DECLARATIONS

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Authors' contributions: All authors contributed equally in the study.

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