The Egyptian Journal of Hospital Medicine (October 2024) Vol. 97, Page 4135-4139

The Impact of Residual Kidney Function on Erythropoietin Responsiveness in Pediatric Patients on Regular Hemodialysis

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ABSTRACT

Background: Anemia is a common complication in children on hemodialysis, and erythropoietin resistance contributes to its management challenges. **Objective:** This study aimed to evaluate the role of residual kidney function (RKF) in predicting erythropoietin responsiveness in pediatric patients on regular hemodialysis.

Methods: This cross-sectional cohort study included 40 children with a mean age of 15 ± 5 years on regular hemodialysis at Sohag University Hospital. The study was conducted from April 2022 to March 2023. Patients were classified as having preserved RKF (urine output >100 mL/m^2/day) or no RKF. Erythropoietin resistance index (ERI), hemoglobin levels, and other clinical and laboratory parameters were compared between the two groups.

Results: Of the 40 patients, 23 (57.5%) had preserved RKF, while 17 (42.5%) did not. Patients with RKF showed significantly higher hemoglobin levels compared to those without RKF (11.71 ± 2.62 g/dL vs. 8.82 ± 1.42 g/dL, $p = 0.002$ respectively) and lower ERI (0.97 ± 0.67 vs. 1.89 ± 1.12 IU/kg/g/dl, $p < 0.002$ respectively). The average erythropoietin dose was significantly lower in patients with RKF (268.3 ± 101.5 IU/kg/week) than in those without RKF (388.5 ± 67.3 IU/kg/week, $p < 0.001$). Growth parameters were better in patients with RKF, with a significant difference in height percentiles ($p = 0.04$). No significant differences were observed in iron profile and metabolic bone parameters, or dialysis adequacy between the two groups. **Conclusions:** Preservation of RKF in pediatric hemodialysis patients is associated with better anemia management, lower erythropoietin requirements, and improved growth outcomes. Strategies to preserve RKF should be emphasized to enhance patient prognosis and quality of life.

Keywords: Residual kidney function, Erythropoietin resistance, Hemodialysis, Anemia, Chronic kidney disease.

INTRODUCTION

Chronic kidney disease (CKD) is an epidemic-scale worldwide health problem that places a significant cost on healthcare systems due to its detrimental impact on cardiovascular health, QOL, and death. In children receiving hemodialysis for end-stage renal disease (ESRD), anemia is a common and serious consequence that lowers QOL and increases morbidity and mortality [1]. In this group, erythropoiesis-stimulating agents (ESAs), such as erythropoietin, are the mainstay of anemia treatment. However, a substantial proportion of patients exhibit ESA hyporesponsiveness characterized by persistently low hemoglobin levels despite high-dose ESA therapy [2].

Increased hospitalization, cardiovascular events, and death are among the negative clinical outcomes linked to erythropoietin resistance [3]. ESA responsiveness is evaluated using the erythropoietin resistance index (ERI), which is computed as the weekly ESA dosage/unit weight and average hemoglobin level [4]. Factors contributing to erythropoietin resistance include iron deficiency, inflammation, hyperparathyroidism, malnutrition, and dialysis inadequacy [5].

It has been demonstrated that residual kidney function (RKF), which is the remaining intrinsic renal function in dialysis patients, is essential to their general health and survival [6].

Better volume control, enhanced potassium and phosphate clearance, decreased inflammation, and increased solute removal are all linked to RKF [7]. However, the impact of RKF on erythropoietin responsiveness in pediatric hemodialysis patients has not been well-characterized. Thus our study aimed to evaluate the role of RKF in predicting erythropoietin responsiveness and to compare the clinical and laboratory parameters between pediatric hemodialysis patients with and without preserved RKF.

PATIENTS AND METHODS

Study design and participants: This cross sectional cohort study was conducted at the Pediatric Nephrology Unit, Sohag University Hospital, Egypt through the period from April 2022 to March 2023. The study included 40 children.

Inclusion criteria: Children aged from 1 to 18 years with CKD on regular hemodialysis for at least 1 year.

Exclusion criteria: Patients with other hematological disorders were excluded.

Data collection: Demographic and clinical data were collected: Age, sex, primary kidney disease, duration of ESRD and dialysis, and dialysis prescription. The presence of RKF was assessed by measuring 24-hour urine output, with RKF defined as a urine output > 100 mL/m^2/day [8]. Patients were divided into two groups according to whether they had RKF or not.

Blood samples were collected pre-dialysis every four months for hemoglobin, serum iron, ferritin, transferrin saturation (TSAT), calcium, phosphate, parathyroid hormone (PTH), and albumin. Kt/V and urea reduction ratio were used to assess dialysis adequacy. URR = BUN − post-dialysis BUN/pre-dialysis BUN.

Received: 05/07/2024
Accepted: 04/09/2024

According to KDOQI guidelines, a minimum URR of 65% is recommended for adequate HD. Kt/V was determined by computer analysis. The Kt/V approach involves multiplying the dialyzer urea clearance (K) by dialysis time (t), then dividing the result by the patient's urea distribution volume (V). The NKF/KDOQI recommendations recommend a Kt/V objective of ≥1.3 for hemodialysis patients and ≥1.7 for peritoneal dialysis patients each week [9].

The weekly erythropoietin dosage per kilogram of body weight per average Hb. level (IU/kg/week/g/dL) was used to compute the ERI [4].

Ethical approval: The Institutional Ethics Committee authorized the study, and the patients' legal guardians gave their informed permissions. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

IBM SPSS 24.0 was used to analyze the data. The Mann-Whitney U test or Student's t-test were used to compare continuous variables, which were reported as mean ± standard deviation or median (IQR). The X^2-test or Fisher's exact test were used to compare categorical variables that were shown as percentages. Spearman's rank correlation coefficient was used to evaluate correlations. P-values ≤ 0.05 were regarded as statistically significant.

RESULTS

In this study, we investigated the role of RKF as a predictor of erythropoietin responsiveness in children undergoing hemodialysis. We compared patients with preserved RKF to those without RKF regarding various clinical and laboratory parameters. The study included 40 patients (20 males, 20 females) with a mean age of 15 ± 5 years. Patients were divided into two groups based on RKF status:

With RKF: (n = 23) (57.5%), **Without RKF: (n = 17)** (42.5%). There were significant differences in age, gender, or consanguinity between the groups. Regarding the groups' ages at dialysis beginning and duration, no discernible differences were discovered (Table 1).

Table (1): Demographic characteristics of patients with and without residual kidney function and dialysis parameters

Characteristic	With RKF (n = 23)	Without RKF (n = 17)	p-value
Age (years)	15 ± 5	15 ± 5	0.6
Gender Male/Female)	13/10	7/10	0.5
Consanguinity (Yes)	15 (65.2%)	10 (58.8%)	0.7
Age at Onset (years)	10 ± 3	10 ± 2	0.9
Duration of dialysis (months)	62 ± 54	69 ± 50	0.7

Erythropoietin dose and resistance index: Patients with RKF required significantly lower erythropoietin doses and had lower ERI values compared to those without RKF (Table 2).

Table (2): Erythropoietin dose and resistance index

Parameter	With RKF (n = 23)	Without RKF (n = 17)	p-value
Average EPO Dose (IU/kg/week)	268.3 ± 11.5	388.5 ± 67.3	<0.001
Average ERI (IU/kg/week/g/dL)	0.97 ± 0.27	1.89 ± 0.12	0.002

Anemia and hematological parameters:

Hemoglobin levels were significantly higher in patients with RKF (11.71 ± 2.62 g/dL) compared to those without RKF (8.82 ± 1.42 g/dL, p = 0.002).

Hematocrit levels were also higher in patients with RKF (34.4 ± 6.7% vs. 27.1 ± 5.1%, p = 0.001). No significant differences were observed in WBC count, MCV, or platelet count (Table 3).

Table (3): Hematological parameters

Parameter	With RKF (n = 23)	Without RKF (n = 17)	p-value
Hemoglobin (g/dL)	11.71 ± 2.62	8.82 ± 1.42	0.002
Hematocrit (%)	34.4 ± 6.7	27.1 ± 5.1	0.001
WBC ($\times 10^3/\mu L$)	6.39 ± 1.51	5.59 ± 1.31	0.3
MCV (fL)	84.8 ± 7.7	85.5 ± 6.4	0.7
Platelets ($\times 10^3/\mu L$)	202.7 ± 50.4	173.1 ± 42.67	0.1

Growth and nutritional status:

Patients with RKF had better height percentiles; 5 (21.7%) had normal height compared to none in the group without RKF (p = 0.04). Weight percentiles and BMI were similar between groups.

Also there was difference between both groups as regards the need for blood transfusion, which was higher in non-residual kidney function group but not reach statistically significance (p value was 0.06).

There was high prevalence of hypertension and ACEI use in patients with no residual kidney function but not reaching statistical significance, [p value was (0.7) (0.7) respectively] (Table 4).

Table (4): Growth parameters

Parameter	With RKF (n = 23)	Without RKF (n = 17)	p-value
Height (Stunted)	18 (78.3%)	17 (100.0%)	0.04
Weight (Underweight)	17 (73.9%)	15 (88.2%)	0.2
BMI (kg/m²)	17.5 ± 3.8	17.7 ± 3.6	0.8
Blood pressure (hypertension)	13 (56.5%)	11 (64.7%)	0.7
ACEI user (yes)	11 (47.8%)	9 (52.9%)	0.7
Blood transfusion (yes)	8 (34.8%)	11 (64.7%)	0.06

Serum albumin levels were similar, indicating comparable nutritional status: With RKF: 3.7 ± 0.4 g/dL, and Without RKF: 3.7 ± 0.6 g/dL (p = 0.9).

Dialysis Adequacy: No significant differences were found regarding urea reduction ratio (URR) and Kt/V values between the groups (Table 5).

Table (5): Dialysis adequacy

Parameter	With RKF (n = 23)	Without RKF (n = 17)	p-value
URR (%)	70.19 ± 8.48	75.02 ± 8.61	0.08
Kt/V	1.43 ± 0.33	1.61 ± 0.35	0.1

Iron profile and metabolic bone parameters: No significant differences were observed regarding iron profile parameters (serum iron, ferritin, transferrin saturation & TIBC), metabolic bone parameters (calcium, phosphorus, magnesium, parathyroid hormone & vitamin D), serum zinc and vit B12 between the groups (Table 6).

Table (6): Iron profile and metabolic bone parameters

Parameter	With RKF (n = 23)	Without RKF (n = 17)	p-value
Serum Iron (µg/dL)	67.6 ± 16.4	65.1 ± 13.3	0.7
Ferritin (ng/mL)	410.0 (min–max: 148.3-1233)	648.3 (min–max: 284.3-1243.6)	0.6
Transferrin Saturation (%)	36.1 ± 4.2	69.9 ± 14.1	0.2
TIBC (µg/dL)	228.7 ± 36.3	238.0 ± 49.7	0.4
Calcium (mg/dL)	9.77 ± 1.99	9.39 ± 1.49	0.5
Phosphorus (mg/dL)	5.3 ± 1.28	4.58 ± 1.12	0.1
Magnesium	2.83 ± 0.43	2.77 ± 0.52	0.6
PTH (pg/mL)	486.1 ± 118.72	628.4 ± 155.51	0.5
Vitamin D (ng/mL)	33.7 ± 7.9	29.2 ± 7.3	0.5
Zinc (mcg/dl)	96.77 ± 23.4	86.35 ± 13.06	0.1
Vit B12 (pg/ml)	433.0 ± 106.7	488.2 ± 119.9	0.4

Median and range: Nonparametric test.

DISCUSSION

The coordinated actions of several elements, most notably the glomeruli, tubular epithelial cells, and interstitial cells, are necessary for native kidney function. There comes a moment at which dialysis is required as an addition to current medical therapy to maintain the patient's health when renal function substantially declines [10].

Endogenous renal functionality, sometimes referred to as RKF, is frequently present in dialysis patients for prolonged periods of time, and the majority of patients have not yet experienced a full stoppage of their native kidney function [11].

The degree and length of the RKF capability differs greatly from patient to patient and is mostly determined by the underlying cause and severity of the kidney impairment, as well as the patient's general health and treatment [12]. To emphasize the significance of comprehending the related advantages of RKF and the available alternatives for RKF measurement, we concentrate on RKF in patients receiving chronic HD in this study.

The purpose of extracorporeal clearance in chronic HD is to remove small molecular-weight solutes and excess water from the blood; it is less effective at removing larger solutes. This limitation is intentionally enforced by technology to prevent the extraction of larger molecules, such as albumin and immunoglobulins, which are essential for vital processes [13].

By eliminating excess acidic metabolites through clearance and adding bicarbonate from the dialysate to balance the plasma pH, HD treats metabolic acidosis. In fact, HD is more efficient than impaired kidneys at eliminating electrolytes and other small-molecular-weight compounds over a specific time period, which is very helpful in urgent clinical situations. This is explained by dialyzers' greater surface area, which usually ranges from 1.5 to 2.5 m^2, as well as their capacity to control dialysis parameters including dialysate and blood flow [14].

Compared to the drastically decreased overall capillary surface area in advanced renal dysfunction, which is only a small portion of the 0.6 m^2 observed in normal kidneys, these characteristics speed up solute transport and elimination [15]. In contrast, endocytosis by tubular epithelial cells in the natural kidneys has a remarkable capacity to remove large-molecular-weight solutes and protein-bound compounds [16]. Additionally, the kidneys' innate capacity to break protein-based connections permits the release, filtration, and consequent excretion of solutes that are bound to proteins. The natural kidneys are therefore very effective in removing protein-bound solutes, which is crucial for preserving the body's homeostatic fluid and electrolyte balance [17].

Our study demonstrated that pediatric patients on regular hemodialysis with preserved RKF exhibited superior anemia control, lower erythropoietin

resistance, and improved growth parameters compared to those without RKF. Patients with RKF showed significantly higher hemoglobin and hematocrit levels and lower erythropoietin resistance index (ERI) values, indicating better responsiveness to ESAs. These results are consistent with the body of research on managing anemia. **Vilar and Farrington** [18] similarly found that RKF independently improves anemia outcomes through enhanced endogenous erythropoietin production and ESA responsiveness. **Ha *et al.*** [19] corroborated these results in children on peritoneal dialysis, demonstrating that preserved RKF was associated with lower ESA requirements and higher hemoglobin levels.

The higher erythropoietin doses and ERI values in patients without RKF reflect increased ESA resistance. **Kalantar-Zadeh *et al.*** [20] revealed that ERI levels were greater in individuals with decreased RKF. While, **Shafi *et al.*** [6] found that RKF was independently related with better hemoglobin levels and lower ESA requirements in adult hemodialysis patients. **Bamgbola** [2] provided context by identifying contributing factors to ESA resistance, including inflammation, iron deficiency, and hyperparathyroidism.

Regarding growth parameters, our study revealed better height percentiles in patients with RKF. **Greenbaum *et al.*** [21] highlighted that malnutrition and hormonal imbalances significantly contribute to growth impairment in pediatric CKD patients. While, **Warady *et al.*** [22] emphasized RKF's role in promoting growth. These studies collectively reinforce the significance of RKF in promoting better growth outcomes. Preserved RKF may improve uremic toxin clearance, fluid balance, and appetite, contributing to better growth parameters. This aligns with **Bonthuis *et al.*'s** [23] review, which emphasizes RKF's role in promoting growth in children on kidney replacement therapy through improved nutritional status and reduced inflammation.

The current study also found that patients with RKF had better height percentiles compared to those without RKF, suggesting a potential relationship between RKF and growth in children undergoing hemodialysis. Also, we found less prevalence of hypertension and ACEI use in patients having residual kidney function. This conclusion is backed up by research by **Bonthuis *et al.*** [23], which reviewed data from patient registries and demonstrated that improvements in CKD management, optimization of dialysis, and advances in transplantation have led to significant improvements in the final height attained by children with CKD and those on kidney replacement therapy (KRT) over time. This study aligns with the current findings, suggesting that RKF may play a role in promoting better growth in children undergoing hemodialysis.

Our study found no significant differences in dialysis adequacy between groups, though Urea reduction ratio (URR) and Kt/V values were slightly higher in patients without RKF. **Termorshuizen *et al.*** [24] reported that RKF significantly contributes to total solute clearance and improved patient survival, independent of dialysis adequacy measures.

Regarding specific metabolic parameters, **Locatelli *et al.*** [5] highlighted the importance of iron status in effective erythropoiesis and ESA responsiveness. In our study, Iron status and metabolic bone parameters showed no significant differences between groups, consistent with **Vilar and Farrington's findings** [18]. This suggests RKF's primary benefits center around erythropoietin responsiveness and growth rather than iron metabolism or bone health. **Al-Hilali *et al.*** [25] reported that secondary hyperparathyroidism is associated with anemia and increased ESA requirements, but our study's similar bone parameters between groups suggest RKF independently influences anemia.

Promoting appropriate blood pressure control, while avoiding intradialytic hypotension, avoiding nephrotoxic agents, beginning with less frequent HD at dialysis initiation and avoiding aggressive dialysis, adopting a low-protein diet, and using biocompatible dialysis membranes and ultrapure dialysate control are some possible methods for maintaining RKF [26].

LIMITATIONS

Study limitations included the single-center design and relatively small sample size, which may affect result generalizability. The cross-sectional nature prevents assessment of long-term outcomes or causal relationships.

CONCLUSION

The RKF is a significant predictor of erythropoietin responsiveness in pediatric patients undergoing hemodialysis. Maintaining RKF in juvenile patients on regular hemodialysis is related with improved anemia treatment, lower erythropoietin resistance, and improved growth parameters. Efforts to preserve RKF should be incorporated into clinical practice to enhance outcomes and QOL in this vulnerable population.

Conflict of interest: None.
Financial disclosures: None.

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