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ORIGINAL ARTICLE

Prevalence and risk factors for functional iron deficiency in children with chronic kidney disease

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Abstract

Introduction Anemia in chronic kidney disease (CKD) is multifactorial. The presence of functional iron deficiency (FID), whereby, there is a block in the transport of iron from macrophage to erythroid marrow is one possible etiology. In this study, we aim to assess the prevalence and risk factors of FID in pediatric CKD.

Methods A cross-sectional study was performed from March to December 2018, after obtaining Institute Ethical Clearance. Children aged ≤ 12 years with CKD, with or without iron supplementation who consented were enrolled. Patients on erythropoietin or on maintenance dialysis were excluded. Details of patients and diseases characteristics were recorded. Various laboratory parameters including complete blood count, red blood cell indices, hypochromic RBC, reticulocyte hemoglobin content, and serum ferritin were measured. Appropriate statistical tests were applied.

Results Out of 174 children, 127 (73%) had structural kidney disease as an etiology of CKD, and 110 (63%) had anemia. Prevalence of anemia was 44%, 43%, 74%, 64% and 92% in CKD stage 1, 2, 3, 4 and 5, respectively. Absolute iron deficiency was found in 66 (38%) even when some children were already on iron supplementation. FID was seen in 44 (25%) and on multivariate analysis, lower estimated glomerular filtration rate and mineral bone disease are associated risk factors.

Conclusion FID is present in one-fourth of our CKD cohort. It should be considered when the response to adequate measures of improving hemoglobin level fails. More studies are required to know its impact on short-term and long-term patient-related outcomes such as quality of life and mortality.

Keywords Anemia · Children · Iron deficiency · Chronic Kidney Disease (CKD) · Functional Iron Deficiency (FID)

Introduction

Many risk factors are associated with the progression of chronic kidney disease (CKD). While hypertension and proteinuria are important modifiable risk factors, others include anemia, hypoalbuminemia and mineral bone disease. Few studied non-modifiable factors for disease progression are genetic predisposition, low birth weight, puberty, propensity of primary disease to progress and ethnicity [1]. Understanding and addressing these factors may help decrease the rate of decline of kidney function. Anemia is one of the commonest complications of CKD reported to affect a variable proportion of children depending upon disease severity [2, 3]. It is an important factor of mortality in CKD [2]. Besides, it is also associated with poor quality of life [4].

Several factors contribute to the development and sometimes, persistence of anemia despite treatment in CKD patients. The various causes of anemia in these children are erythropoietin deficiency, lack of substrate (iron, vitamin deficiency B12 and folate), ongoing inflammation, blood loss because of multiple sampling or during hemodialysis, and hyperparathyroidism. Usually, these are treatable with various agents [2].

Functional iron deficiency (FID), on the other hand, is the state of insufficient iron utilization by bone marrow erythroid precursor cells despite adequate iron stores. The amount of stainable iron content in bone marrow and ferritin level is normal in an individual in this state. It is the result of a block of iron transport to erythroid marrow [5]. It is seen in

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conditions like inflammation, malignancies, and infections. However, there are reasons to believe that CKD patients may be having this condition, which adds up to the difficulty in treating anemia in these patients [5, 6]. As there is a dearth of literature on FID in children with CKD, we wanted to assess its prevalence and associated risk factors.

Methods

This cross-sectional study was conducted in the pediatric nephrology unit of a tertiary care hospital in North India, after obtaining ethical clearance from the Institute Ethics Committee (INT/IEC/2018/000272). This study was conducted from March 2018 to December 2018. All consecutive children presenting for the first time to the pediatric nephrology clinic were assessed for eligibility. We enrolled children aged less than 12 years with a diagnosis of CKD, who were not on erythropoietin. Children who have been started on iron therapy elsewhere were enrolled. Children with chronic liver disease and on kidney replacement therapy were excluded from the present study. Parents of CKD children, who satisfied the above eligibility criteria, were invited to participate in the study, and consent (assent, wherever applicable) was obtained.

A detailed case record sheet including demographic details, disease course, and physical examination was carried out for every child. Approximately 2.0–2.5 ml EDTA and plain sample each were withdrawn from patients. EDTA sample was run on an automated hematology analyzer (Sysmex XN-1000; Japan) for complete blood count (CBC), red blood cell (RBC) indices, and newer RBC and reticulocyte parameters [Hypochromic RBC (%HRC) and reticulocyte hemoglobin content (CHr)]. The other sample was processed on an automated chemistry analyzer (Advia Centaur; Siemens) for serum ferritin. We also measured serum levels of creatinine, calcium, phosphate, alkaline phosphatase, vitamin D, and parathyroid hormone (PTH) using ADVIA 1800.

CKD was defined and staged as per KDIGO criteria [7]. In children, less than 2 years of age, calculated GFR based on serum creatinine was compared with normative age-appropriate values [8]. Anemia was defined as per KDIGO recommendations when hemoglobin was < 11 g/dL for children aged 6 months to 5 years and < 11.5 g/dL in those ≥ 5–12 years [7]. Iron deficiency was defined as serum ferritin < 100 ng/ml and transferrin saturation < 20% [7]. Functional iron deficiency anemia was defined when anemia was present with HRC > 6%, or CHr < 29 pg and serum ferritin of > 100 ng/ml [5, 6]. The estimated glomerular function rate (eGFR) was calculated by the standard Bedside Schwartz formula as eGFR = k x-height of the child (cm)/serum creatinine (mg/dL) [9]. Wasting was defined as weight for height below −2 *Z* score (more than two standard deviations below the median population using WHO growth charts). Stunting was defined as height for age below −2 *Z* score (more than two standard deviations below the median population using WHO growth charts) [10, 11]. CKD-Mineral Bone Disease (CKD-MBD) was considered when any one of the following given criteria met:

- Laboratory abnormalities- abnormalities in calcium, phosphorus, PTH, or vitamin D metabolism or
- Bone abnormalities–changes in bone turnover, mineralization, volume, linear growth or strength or
- Calcification in soft tissue or vessel [12].

Statistical analysis

Statistical analysis was performed by STATA version 14.2 using the chi-square test of independence. Descriptive statistics, frequency, and percentages were calculated to present all categorical variables including sex, age group, etiology of CKD, clinical features, and laboratory parameters.

Numerical values were summarized by mean ± SD and Interquartile Range (IQR). Chi-square, and Mann–Whitney test was used to compare binary and continuous outcomes as appropriate. We used logistic regression analysis to assess the risk factors for absolute and functional iron deficiency anemia in children with CKD. For multivariate logistic regression, covariates with *P* values < 0.20 on univariate logistic regression were included.

Results

A total of 174 children were included in the study. The baseline characteristics of the patients are depicted in Table 1. The mean age of included patients was 6.4 ± 4.0 years and 77.5% of patients were boys. A maximum number of children were in the group where the age at presentation was > 9–12 years. The most common cause of CKD was structural kidney diseases, that is congenital anomalies of the kidney and urinary tract (CAKUT) followed by glomerular diseases. In 16% of patients, the underlying etiology could not be confirmed. Stunting was present in 55% while 15% also had wasted. Clinical pallor on examination was seen in 129 (74%) and 52 (29%) had rickets or bony abnormalities. Overall, 99 (56%) patients had eGFR less than 60 ml/min/1.73 m^2 and 20% patients had CKD stage-5 in pre-dialysis state. Hypertension was observed in 149 (85%) at the time of assessment.

Prevalence and risk factors for anemia

Of the 174 patients with CKD, 110 (63%) patients had anemia. A higher proportion of children had anemia with

Table 1 Baseline characteristics of participants

Variables	Total patients *n* (%) *N* = 174
Age (mean ± SD)	6.4 ± 4.0
< 3 years	46 (26)
3 to ≤ 6 years	26 (15)
> 6 to ≤ 9 years	39 (22)
> 9 years	63 (36)
Sex	
Boys	135 (77.5)
Girls	39 (22.5)
Etiology	
CAKUT	127 (73)
Glomerular disease	9 (5)
Cystic kidney disease	4 (2)
Neurogenic bladder	6 (4)
Unknown	28 (16)
CKD stages	
1	54 (31)
2	21 (12)
3	35 (20)
4	28 (16)
5	36 (20)
Growth parameters	
Stunting	95 (55)
Wasting	25 (15)
Complication of CKD*	
Anemia	110 (63)
CKD-MBD	95 (55)
Hypertension	149 (85)
Metabolic acidosis	141 (81)

CAKUT congenital anomaly of kidney and urinary tract, *CKD-MBD* chronic kidney disease-mineral bone disorder

*Complication as assessed at the time of enrollment in the study

increasing severity of CKD. Prevalence of anemia was 44%, 43%, 74%, 64% and 92% in CKD stage 1, 2, 3, 4 and 5, respectively. Prevalence of anemia was significantly higher in children with eGFR less than 60 ml/min/1.73 m^2 (77%) compared to those with eGFR more than 60 ml/min/1.73 m^2 (33%) ($P < 0.001$). Median hemoglobin levels (11.4–11.5 g/dL) were near normal in CKD stages 1 and 2 as compared to very low levels (7.8 g/dL) in CKD stage 5. On univariate regression analysis, the presence of CKD-MBD, stunting, wasting, metabolic acidosis, and lower GFR was associated with anemia in these children. However, only CKD-MBD, stunting, and lower eGFR were significant risk factors for anemia found in multivariate regression analysis (Table 2).

Prevalence and risk factors for absolute and functional iron deficiency

Overall, 20% of children with CKD had HRC > 6% and CHr less than 29 pg was observed in 62% of children. High ferritin level (> 100 ng/ml) was found in 35% of children. Further analysis showed that 37%, 38% and 25% of patients were categorized as having no iron deficiency (NID), absolute iron deficiency (AID), and functional iron deficiency (FID), respectively (Table 3). As children on iron supplementation were also enrolled, the AID may be an underestimate. FID was more common in older children (aged > 9 years) and those with glomerular disease as the underlying etiology of CKD (Table 3). It was more common in children with eGFR less than 60 ml/min/1.73 m^2 (38%) compare to those with eGFR more than 60 ml/min/1.73 m^2 (11%) ($P < 0.001$). The proportion of children having FID was significantly higher in those having metabolic acidosis and CKD-MBD (Table 3).

In univariate regression analysis, lower eGFR and the presence of CKD-MBD were associated with FID. These risk factors remain significant after adjusting for multivariate logistic regression analysis (Table 4). Metabolic acidosis was the only significant risk factor observed in this study in children with CKD for AID (Table 4). The frequency of iron status across the various stage of CKD is depicted in Fig. 1.

Table 2 Risk factors for anemia in children with pre-dialysis CKD

Risk factor	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.01 (0.94–1.109)	0.94		
Sex	0.91 (0.43–1.9)	0.80		
Wasting	3.5 (1.15–10.8)	0.02		
Stunting	1.1 (0.6–2.2)	< 0.001	2.9 (1.4–6.1)	0.06
eGFR	0.98 (0.97–0.99)	< 0.001	0.99 (0.98–0.998)	0.02
Etiology	1.2 (0.94–1.5)	0.15		
Hypertension	0.82 (0.52–1.3)	0.52		
Metabolic acidosis	2.5 (1.1–5.4)	0.02		
CKD-MBD	6.0 (3–11.7)	< 0.001	5 (2.2–12)	< 0.001

eGFR estimated glomerular filtration rate, *CKD-MBD* chronic kidney disease-mineral bone disease

Table 3 Comparison of various parameters across various categories of iron deficiency

	No iron deficiency ($n=64$)	Absolute iron deficiency ($n=66$)	Functional iron deficiency ($n=44$)	*P* value
Age				
< 3 years	20 (43)	19 (41)	07 (15)	0.03
3 to ≤ 6 years	09 (35)	12 (46)	05 (19)	
> 6 to ≤ 9 years	13 (33)	17 (44)	09 (23)	
> 9 years	22 (35)	18 (29)	23 (30)	
Sex				
Boys	51 (37)	52 (39)	33 (21)	0.66
Girls	13 (33)	14 (36)	11 (31)	
Etiology				
CAKUT	50 (39.5)	50 (39.5)	27 (21)	0.07
Glomerular disease	1 (11)	3 (33)	5 (56)	
Cystic kidney disease	2 (50)	2 (50)	0	
Neurogenic bladder	0	2 (33)	4 (67)	
Unknown	11 (39)	9 (32)	8 (29)	
CKD stages				
1	28 (52)	20 (37)	06 (11)	< 0.001
2	11 (52)	7 (33)	3 (15)	
3	10 (28)	16 (46)	09 (26)	
4	11 (39)	14 (50)	3 (11)	
5	4 (11)	09 (25)	23 (64)	
Growth parameters				
Normal height	36 (45)	26 (33)	17 (22)	0.09
Stunting	28 (30)	40 (42)	27 (28)	
No wasting	60 (40)	53 (36)	36 (24)	0.06
Wasting	4 (16)	13 (52)	8 (32)	
Complication of CKD				
No CKD-MBD	47 (59)	25 (32)	07 (09)	0.001
CKD-MBD	17 (18)	41 (43)	37 (39)	
No hypertension	07 (28)	08 (32)	10 (40)	0.22
Hypertension	57 (38)	58 (39)	34 (23)	
No metabolic acidosis	18 (55)	10 (30)	05 (15)	0.05
Metabolic acidosis	46 (33)	56 (40)	39 (27)	

Table 4 Risk factors for absolute iron deficiency and functional iron deficiency, respectively, in children with pre-dialysis CKD

Risk factor	Functional iron deficiency				Absolute iron deficiency			
	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.06 (0.98–1.16)	0.11			1.0 (0.92–1.08)	0.95		
Sex	1.85 (0.88–4.0)	0.10			0.8 (0.40–1.7)	0.60		
Wasting	1.5 (0.62–3.7)	0.34			0.78 (0.36–1.9)	0.60		
Stunting	1.1 (0.6–2.2)	0.67			1.1 (0.6–2.0)	0.73		
eGFR	0.98 (0.97–0.99)	0.001	0.99 (0.98–0.99)	0.04	1.0 (0.98–1.05)	0.99		
Etiology	1.1 (0.88–1.3)	0.40			1.1 (0.87–1.3)	0.54		
Hypertension	0.73 (0.48–1.1)	0.15			0.80 (0.53–1.2)	0.30		
Metabolic acidosis	1.6 (0.6–4.0)	0.3			0.34 (0.15–0.75)	0.007	0.30 (0.13–0.67)	0.004
CKD-MBD	5.0 (2.2–10.4)	< 0.001	3.5 (1.7–9.0)	< 0.001	1.4 (0.7–2.5)	0.33		

eGFR estimated glomerular filtration rate, *CKD-MBD* chronic kidney disease-mineral bone disease

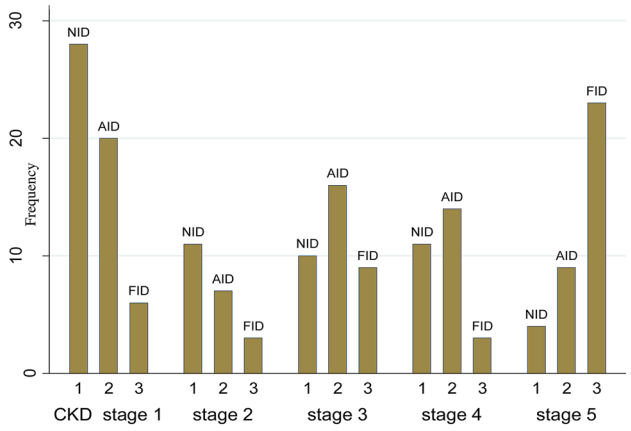

Fig. 1 Frequency of iron status among children with chronic kidney disease. *NID* no iron deficiency, *AID* absolute iron deficiency, *FID* functional iron deficiency

Discussion

Anemia is one of the chief complications of CKD. While erythropoietin deficiency is the chief cause, iron deficiency and chronic inflammation are also significant contributory factors. Aggressive management of anemia avoids repeated blood transfusion and also improves cognitive function, cardiovascular function as well as quality of life. FID is the state of insufficient iron utilization by bone marrow erythroid precursor cells despite adequate iron stores [2, 4–6].

In this cross-sectional study, we found that anemia was present in 63% of children. Lower eGFR, stunting, and the presence of CKD-MBD were significant risk factors for anemia in these children. Absolute iron deficiency was observed in 38% of children, even though patients on iron supplementation were not excluded from the study. Metabolic acidosis was the only risk factor associated with an absolute deficiency of iron. FID was detected in one-fourth of children enrolled in this study. The presence of CKD-MBD and lower eGFR were the main risk factors associated with FID in this cohort.

The prevalence of anemia in the present study was higher than previously reported in various studies [3, 13, 14]. A study from (KNOW-PedCKD study) Korea evaluated children with CKD stages 1–5 and found the prevalence of anemia to be 39.7%. A possible explanation for the higher prevalence in our cohort is poor dietary intake and micronutrient deficiency. As reported previously by Atkinson et al., the prevalence of anemia increase with a higher stage of CKD [15]. In the present study, the prevalence of anemia in CKD stage 3 was 74%, which is almost similar to data reported by Atkinson et al. [15]. The reported risk factors for anemia in literature are level of kidney function, low albumin, glomerular etiology, and low body weight [2, 13]. However, in this study, we found that stunting, CKD-MBD, and level of kidney dysfunction were risk factors for anemia in children with pre-dialysis CKD. While stunting indirectly may indicate inadequate nutrition and severity of disease, the decline in GFR has been reported previously to be associated with an increased prevalence of anemia. The presence of the CKD-MBD is associated with high PTH which may affect the erythropoiesis in these children with CKD [16].

We observed FID in 25% of children with CKD and prevalence was higher in children with eGFR less than 60 ml/min/1.73 m^2. Children with CKD stage 5 had the highest prevalence of 64%. This can be explained because end-stage kidney disease patients tend to have higher inflammation and higher hepcidin levels both of which are linked to a functional iron deficiency state [17, 18]. Previously, a study by Goyal et al. reported that marker of inflammation such as C-reactive protein increases with increasing stages of CKD [19]. The same study also demonstrated that hepcidin levels were highest in children with impaired iron trafficking.

While there is a paucity of data in the pediatric population on FID in CKD, some adult studies suggest a lower prevalence of FID compared to the present study. In a large study by Awan et al., they evaluated 933,463 patients with CKD stage 3–4 and found that the prevalence of FID was 19% [20]. Another study reported a lower proportion of patients (7.9%) to have an FID as compared to the present study [21]. However, a study by Plastina et al. evaluated 183 patients on hemodialysis and found FID in almost every third patient (37%) [22]. Similarly, a study from South Africa also reported a higher prevalence (42.9%) of FID in adult patients. Similar to the study by Awan et al. [20], we also found that the advanced stage of CKD was a risk factor for FID. We also observed the presence of mineral bone disease as an important risk factor for FID.

While we comprehensively evaluated all parameters to assess the iron stored in the body, the study has a few limitations. Firstly, we did not assess the impact of FID on quality of life, cardiovascular morbidity, or mortality in these patients. We also did not assess the hepcidin levels or other inflammatory markers like CRP and their correlation with functional iron deficiency status.

Conclusion

In summary, we observed that the burden of absolute and functional iron deficiency is considerable in children presenting with CKD, more so in those with advanced stages. We also found that CKD-MBD is an important risk factor for FID and metabolic acidosis for AID. The result from this study suggests that every 4th child with CKD may have FID. Hence, it should be considered when children with CKD fail to respond after adequate measures of improving hemoglobin levels. Further studies are needed to assess the

burden of FID in children on dialysis as well as its impact on short-term and long-term patient-related outcomes such as quality of life and mortality.

Declarations

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional ethics committee at which the studies were conducted (INT/IEC/2018/000272) and 1964 Helsinki declaration and its later amendments.

Informed consent We provided all individual patients with the option to opt-out of participation.

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