Functional iron deficiency in children with Chronic Kidney Disease presenting to a tertiary center

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ABSTRACT

Background *: Anemia is one of the most common and clinically significant complications of Chronic Kidney Disease (CKD) in children and is associated with a variety of adverse clinical consequences, including an increased risk for hospitalization and mortality. The predominant causes are erythropoietin deficiency, lack of iron availability, inflammation, blood loss, hyperparathyroidism, and vitamin deficiency B12 and folate. Functional iron deficiency (FID), is the state of insufficient iron utilization by bone marrow erythroid precursor cells despite adequate iron stores.* ***Methods:*** *This was a cross sectional study conducted in the Department of Pediatrics, PGIMER, Chandigarh, India from July 2017 to December 2018 consisting 190 patients after ethical clerance from institutional Ethic committe. The demographic and clinical details were taken and laboratory investigation regarding, hemogram, iron profile, Calcium, phosphorous, Vitamin D, Parathyroid hormone, Venous blood gas were done. The analysis was done by SPSS version 16.* ***Results:*** *Out of 190 patients enrolled in the study 145 were male and 45 females. CKD was more common in boys with a sex ratio of 3.2:1 and mean age of diagnosis of CKD was 6.49±4.04 years. The most common stage of CKD at presentation was stage I CKD 32.6% (N=62) followed by stage III CKD 19.5% (N=37) and stage V CKD 19.5% (N=37).Most of them had structural kidney disease. Anemia was present in in 62.6% (N=119). The prevalence of functional iron deficiency in our children was 38.37% (N=66) out of 172 CKD children tested) of CKD children. Percentage of hypochromic red cells(HRC) >6 % was present in 29 patients (out of 142 tested). Reticulocyte hemoglobin content (CHr) <29 pg in 97 CKD children (out of 140 tested). 54 patients had ferritn level >100 ug/L if not on dialysis and >200 ug/L if on dialysis (out of 153 tested).* ***Conclusions****: CKD was more common in boys with etiology being structural kidney disease. The prevalence of functional iron deficiency was 38.37%. This number signifies that significant number of our CKD children are anaemic. We emphasis the need to improve multiple aspects of CKD management, including early diagnosis and treatment of anemia.*

Keywords*: Functional iron deficiency (FID); Chronic Kidney Disease(CKD);Anemia; Pediatric*

1. INTRODUCTION

Anemia is a major complication in children with chronic kidney disease (CKD). The various causes of anemia in CKD children are erythropoietin deficiency, lack of substrate (iron, vitamin B12 and folate), ongoing inflammation, blood loss because of multiple sampling or hemodialysis and hyperparathyroidism.[1] Functional iron deficiency (FID), is the state of insufficient iron utilization by bone marrow erythroid precursor cells despite adequate iron stores.It is the result of block of iron transport to erythroid marrow.[2]

Risk factors like antenatal renal abnormalities, hereditary kidney disease, neonatal acute kidney injury (AKI) or a low birth weight(LBW), recurrent UTI associated with reflux, nephritis or nephrotic syndrome,lower urinary tract obstruction, uncontrolled diabetes, hypertension, autoimmune disease (like Systemic Lupus Nephritis), HIV infection, NSAIDs or any nephrotoxic drugs can lead to CKD.[3]

There are very few studies in children with CKD.Thus, we want to study the prevalence of FID and various etiologies of CKD in patients presenting to our centre. We envisage that knowledge of the above will sensitize us with the common etiologies of CKD, thus help us to detect these diseases and complications earlier.

2. METHODOLOGY

This was a cross sectional study conducted in the Department of Pediatrics (Pediatrics Nephrology Unit, Advanced Pediatrics Centre), Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India from July 2017 to December 2018.The participants of the study was children till 12 years of age who attended the renal outpatient clinic, and pediatric Nephrology ward at this institute. The ethical clearance for this study was taken from Institutional Ethic Committee Reg.No. 272. of PGIMER, Chandigarh. All consecutive children presenting with the inclusion criteria and consenting to be part of the study were included.

Inclusion criteria

Children till 12 years of age with CKD. CKD defined by, when either of following criteria were present: Criteria 1: Kidney damage for ≥ 3 months as defined by structural and functional abnormalities of kidney with or without decrease GFR manifested by one or more of the following features: Abnormalities in the composition of blood or urine, abnormalities of imaging test, abnormalities in kidney biopsy. **OR** Criteria 2: GFR<60 ml/min/1.73m2 for ≥3 months, with or without the other sign of kidney damage as described above. **OR** Criteria 3: In children less than 2 years of age calculated GFR based on serum creatinine can be compared with normative age appropriate values.[4]

Exclusion criteria: All children with malignancies and chronic liver disease (CLD).

Parents of CKD children, who satisfy the above eligibility criteria, and giving written informed consent was enrolled in the study. Details was recorded in a pre-designed case record form. Demographic details were recorded, presenting complains,examination was done. The weight of the child was taken by a digital weighing machine (Digitome) and was recorded.

 Wasting defined as weight for height below -2 Z score (more than two standard deviation below the median population using WHO growth charts).[5]

 Stunting defined as height for age below -2 Z score (more than two standard deviation below the median population using WHO growth charts).[6]

An appropriate size blood pressure cuff was used to take blood pressure of the Children.[7] The children were considered to have hypertension if resting systolic and or diastolic BP value equals or exceeds 95th percentile of according to gender, age, and height as per AHA guidelines.[8] The routine investigations done for all CKD children was done and noted. This included

1. Complete Blood Count; peripheral blood smear; percentage of hypochromic RBCs (%HRC); reticulocyte hemoglobin content (CHr):

 Anemia defined as per KDIGO guidelines recommendations [9] when haemoglobin (Hb) value (a) in 0.5 to <5 years was <11 g/dl; (b) in those from 5 to 12 years when Hb < 11.5 g/dl.

 Functional iron deficiency(FID) defined when anemia is present with (a) % of hypochromic red cells (% HRC) >6%, or (b) reticulocyte Hb content (CHr) <29 pg or (c) serum ferritin of >200ug/L if on hemodialysis, or >100ug/L if not on hemodialysis.[1] (Normal range for CHr is 29.5-32.5 pg and that for % HRC is <2 %.)

2. Biochemical profile

 Hypo or hypercalcaemia: total calcium (mg/dl) is not full filing the range as per age;[10] 1-5 years: 9.2-10.2. 6-12 years: 9.32-10.32. *Hypo or hyperphosphatemia*: phosphate(mg/dl) is not full filing the range as per age; [10] 1-5 years: 4.33-6.47. 6-12 years: 3.40-5.78. *Calcium phosphate product*:≤12 years:≥ 65mg2/dl2 was considered abnormal.[10] *High alkaline phosphatase*: phosphate range greater than age appropriate Value [9] 1-5 years: 100-350U/L 6-12 years: 60-450U/L . *Hypo or hyperparathyroidism*: parathyroid hormone (pg/ml) not within normal range of 15 to 65 pg/ml. *eGFR*: estimated glomerular function rate of the child, which is calculated by the

standard Schwartz' formula [4] as eGFR= k x height of the child (cm) / sCr Where value of k is constant. It is determined empirically by Schwartz and associates. It is taken as, □ 0.45 for term infant during first year of life, □ 0.55 for children and adolescent girl and □0.75 for adolescent boys.

3. Venous blood gas:

Metabolic acidosis defined if [10] a) Arterial/Venous pH<7.35 with b) Plasma bicarbonate <22 mmol/L among children >2 years of age or <20 mmol/L among <2 years of age.

4. Serum ferritin level:

Based on this value along with HRC and CHR patient is classified as FID.

5. Vitamin D/iPTH:

□ *Vitamin D sufficiency* defined as serum 25(OH) D greater than 30ng/ml, *Vitamin D insufficiency* defined as serum 25(OH) D at 20-30 ng/ml and *Vitamin D deficiency* with level less than 20 ng/ml.[11] *Hypo or hyperphosphatemia*: phosphate(mg/dl) not within age appropriate. Range [9] □ 1-5 years -*4*.3-6.47, □ 6-12 years:3.4-5.8 [10] Based on the biochemical and endocrine reports patient is classified as

Mineral Bone Disorder: CKD mineral bone disorder is the constellation of clinical,biochemical and imaging abnormalities associated with CKD. If any one of the following given criteria met i.e. laboratory abnormalities-abnormalities in calcium, phosphorus , PTH, or vit D metabolism □bone abnormalities–changes in bone turnover, mineralization, volume, linear growth or strength and calcification in soft tissue or vessel. [12]

6. **Urinalysis (Routine and microscopy):** To detect albuminuria and/or hematuria.

7. STATISTICAL ANALYSIS:

Data including age, gender, etiology of CKD, hemoglobin, % HRC, CHr, Ferritin and other variables were entered in Microsoft excel sheet. Statistical analysis was performed by SPSS version 16 using chi-square test of independenc. Descriptive statistics, frequency and percentages was calculated to present all categorical variables including sex, age group, etiology of CKD, clinical features and laboratory parameters.Numerical values were summarized by medians and ranges. The Spearman correlation coefficient was used to determine the monotone function between serum ferritin and % HRC.

4. RESULTS

Baseline demographics of CKD patients:

A total of 190 children who fulfilled the inclusion criteria and consented were included in the study. These children were further subdivided into four age groups as <3 years, 3 to <6 years, 6 to <9 years and 9 to 12 years. Boys predominate in our study with a percentage of 76.3% with sex ratio of 3.2:1.The mean age of patients enrolled in the study is 6.49 ± 4.041 years. Maximum number of children came from Punjab 86 followed by Haryana 32,chandigarh 23,Himacal Pradesh 21,Uttar Pradesh 7,Rajasthan 2,Uttrakhand 2,West Bengal 1,Bihar 2,Delhi 2, OTHERS 4 . Baseline demographics of CKD patients is given in Table 1.

Table 1. Baseline demographics of CKD patients

Variables	**Frequency**	**Percentage (%)**
Sex male/female	145 / 45	76.3 % / 23.7 %
Age group		
<3	49	25.8 %

3 to <6	28	14.7 %
6 to <9	44	23.2 %
>9 to 12	69	36.3 %
Total	190	100 %
Etiology Of CKD		
Vesico urethral reflux	32	17%
Posterior urethral valve	31	16%
Multi cystic dysplastic kidney (MCDK)	24	13%
Pelvi ureteric junction Obstruction	11	6%
Neurogenic Bladder	6	3%
Autosomal Recessive Polycystic Kidney disease	5	3%
Others	81	43%
CKD Stages		
i	62	32.6%
ii	23	12.1%
iii	37	19.5%
iv	31	16.3%
v	37	19.5%

Table 2. Symptoms and clinical examination findings

Variables	**Frequency**	**Percentages**
Symptoms		
Appetite	119	62.6%
Failure to thrive	115	60.5%
Pallor	103	54.2%

Decrease urine output	65	34.2%
Vomiting	54	28.4%
Increased urine output	33	17.4%
Headache	31	16.3%
Swelling of body	21	11.1%
Hematuria	7	3.7%
Encephalopathy	12	6.3%
Examination Findings		
Wasting	27	14.2%
Stunting	104	54.8%
Severe Stunting	71	37.4%
Overweight	5	2.6%
Underweight	19	10%
Hypertension	52	27%
Pallor	129	67.9%
Edema	14	7.4%
Ricket/Bony abnormalities	52	27.4%

Distribution of etiology in different stages of CKD

Out of 62 with stage I CKD, the most common etiology in were MCDK (N=14) followed by PUV (N=9) and VUR (N=9). The least common etiology was neurogenic bladder (N=1). Out of 23 with stage II CKD, the most common etiology in were PUV (N=7) followed by VUR (N=5) followed by MCDK (N=2). The least common etiology was immune complex mediated crescentric glomerulonephritis (N=1). Out of 37 with stage III CKD, the most common etiology in were PUV (N=7) followed by VUR (N=4) and MCDK (N=4). The least common etiology was ARPKD (N=1), obstructive uropathy (N=1), neurogenic bladder (N=1). Out of 31 with stage IV CKD, the most common etiology in were PUV (N=6) andVUR (N=6). The least common etiology was and MCDK (N=1) renal dysplasia (N=1), thrombotic microangiopathy with cortical necrosis (N=1), solitary kidney (N=1), neurogenic bladder (N=1). Out of 37 with stage V CKD, the most common etiology in were VUR (N=8) followed by MCDK (N=3), PUV (N=2), PUJ obstruction (N=2). The least common etiology was crescentric glomerulonephritis (N=1), CKD following malarial episode with AKI (N=1), neurogenic bladder (N=1), pyelonephritis (N=1), HUS (N=1), solitary cystic kidney (N=1).

Table 3. Distribution of CKD patients as per investigation:

Lab Parameters	Frequency	Percentage	Remarks
Anemia	119	62.6%	190 Tested
Reticulocyte Hb content < 29 pg	97	69.3%	140 tested

Hypochromic RBC >6%	29	20.4%	142 tested
Ferritin >100 not on dialysis	99	64.70%	153 tested
Ferritin >200, if on dialysis	54	35.3%	153 tested
Functional Iron Deficiency	66	38.4%	172 tested
Hypo Calcemic	102	53.7%	77(40.5%) normocalcemic
Hyper calcemic	11	5.8%	
Hypo Phosphatemia	21	11.1%	127(68.8%)normal phosphorous
H yper Phosphatemia	42	22.1%	
Calcium phosphate product >64.5	13	7%	
Alkaline phosphate	25	13.2%	
Vit D insufficient amount	37	31.1%	Sufficient Vit D in 59(31.1%)
Vit D deficient amount	94	49.5%	
Parathyroid hormone increased	95	50%	Nomal parathyroid level 90(47%)
Parathyroid hormone decreased	5	3%	
Mineral bone disorder	101	53.16%	
Metabolic acidosis	152	80%	
Urine abnormality proteinurea/hematuria)	52	27.4%	

Table 4. Distribution of Anemia in different stages of CKD

CKD	**Variables**	**Laboratory Anemia**		**Total**
		No	**Yes**	
Stage 1	Count	34	28	62
	%within stage of CKD	54.8%	45.2%	100%
	%with laboratory Anemia	47.9%	23.5%	32.5%
ii	Count	14	9	23

	%within stage of CKD %within Functional Iron Deficiency	60.9% 19.7%	39.1% 7.6%	100% 12.1%
iii	Count %within stage of CKD %within Functional Iron Deficiency	9 24.3% 12.7%	28 75.7% 23.5%	37 100% 19.5%
iv	Count %within stage of CKD %within Functional Iron Deficiency	10 32.3% 14.1%	21 67.7% 17.6%	31 100% 16.3%
v	Count %within stage of CKD %within Functional Iron Deficiency	4 10.8% 5.6%	33 89.2% 27.7%	37 100% 19.5%
Total	Count %within stage of CKD %within Functional Iron Deficiency	71 37.4% 100%	119 62.6% 100%	190 100% 100%

Distribution of functional iron deficiency in different stages of CKD

Functional iron deficiency/FID was considered when anemia was present with a) % of hypochromic red cells (% HRC) >6% OR b) reticulocyte Hb content (CHr) <29 pg OR c) serum ferritin of >200ug/L if on hemodialysis or >100ug/L if not on hemodialysis.[1] 119 CKD children had anemia (out of 190 tested), 97 children had reticulocyte haemoglobin content <29pg (out of 140 tested); 29 patients had hypochromic red cell >6% (out of 142 tested) and 54 had ferritn level >100 ug/L if not on dialysis and >200 ug/L if on dialysis (out of 153 tested). FID was present in 38.4% (N=66) out of 172 CKD children tested) of CKD children.The distribution of functional iron deficiency in stage I CKD was 19.7% (N=13); stage II CKD was 9.1% (N=6); stage III CKD was 21.2% (N=14); stage IV CKD was 10.6% (N=7) and stage V CKD was 39.4% (N=26).Functional iron deficiency in CKD Children is given in Table 5.

Table 5. Distribution of functional iron deficiency in different stages of CKD

CKD	Variables	Functional Iron Deficiency		Total
		Yes	No	
Stage 1	Count	41	13	54
	%within stage of CKD	75.9%	24.1%	100%
	%within Functional Iron Deficiency	38.7%	19.7%	31.4%
ii	Count	14	6	20
	%within stage of CKD	70%	30%	100%
	%within Functional Iron Deficiency	13.2%	9.1%	11.6%
iii	Count	20	14	34
	%within stage of CKD	58.8%	41.2%	100%
	%within Functional Iron Deficiency	18.9%	21.2%	19.8%
iv	Count	21	7	28
	%within stage of CKD	75%	25%	100%
	%within Functional Iron Deficiency	19.8%	10.6%	16.3%
v	Count	10	26	36
	%within stage of CKD	27.8%	72.2%	100%
	%within Functional Iron Deficiency	9.4%	39.4%	20.9%
Total	Count	106	66	172
	%within stage of CKD	61.6%	38.4%	100%
	%within Functional Iron Deficiency	100%	100%	100%

Distribution of Mineral bone disorder in different stages of CKD

Mineral bone disorder was present in 17.8% (N=18) of stage I CKD; 8.9% (N=9) of stage II CKD; 19.8% (N=20) of stage III CKD; 23.8% (N=24) of stage IV CKD and 29.7% (N=30) of stage V CKD**.**

Distribution of Metabolic Acidosis disorder in different stages of CKD

Metabolic acidosis was present in 23% (N=35) of stage I CKD; 13.8% (N=21) of stage II CKD; 22.4% (N=34) of stage III CKD; 18.4% (N=28) of stage IV CKD; 22.4% (N=34) of stage V CKD**.**

Table 6: Distribution of Lab investigations in all stages of CKD.

Investigations	Mean	Standard deviation	Range
Blood Urea	77.25	69.2	341-8
Creatinine	3.1	15.2	0.1-208
Haemoglobin	10.19	2.48	3.2-16.1
TLC	10,459	6,996	1,081-64,600
Platelets counts	3,01,000	1,15,000	18,000-7,23,000
MCV	80.6	8.12	53.6-100
MCHC	32.3	2.7	14.6-48
MCH	25.2	1.48	22-31
RDW	17.04	2.13	12.8-22.4
CHR	26.8	4.11	0.2-33.5
HRC	3.69	6.8	0.08-45
Ferritin	150.7	266.5	1.1-1797
S. Iron	75.73	59.5	9.2-343.4
TIBC	304.1	93	5.4-575.3
% Saturation	28.1	33.2	3.2-281
Calcium	8.9	1.24	2.7-11.7
Phosphate	5.2	1.42	1.2-12.4
Ca X PO4	46.3	12.8	7.2-92.1
ALP	293	174	105-1570
Vitamin D	23.7	16.75	2.6-70
Parathyroid	211.2	330	3.9-1652
PH	7.32	0.1	6.9-7.6

HCO3	18.5	3.9	3.7-27
eGFR	72.8	60.1	4.6-308

5. DISCUSSION

This is a cross sectional study conducted on total of 190 children with CKD who visited the hospital during the period of July 2017 to December 2018. We evaluated the distributions of data as per age, sex, address, clinical complaints, examination findings (weight, height, BMI, BP, pallor, edema and rickets), anemia and status of functional iron deficiency besides other investigations in these children. We also tried to find the prevalence of different stages of CKD and the various etiologies.

Out of 190 CKD children, 145 children were male, with a sex ratio of 3.2:1. The mean age of presentation was 6.49±4.04 years. Bek K et al had reported from 29 centres with 282 patients (159 male) a sex ratio of 1.3 and a mean age of presentation as 8.05±5.25 years.[13] Similarly, Hiep T et al reported 143 CKD children who had a mean age of presentation as 3 years with a sex ratio (82 male) of 1.3.[14] Hari et al reported 305 CKD children with a mean age of presentation as 8 years and a sex ratio (225males) of 2.8.[15] The mean age of presentation of CKD in our study was more or less comparable to various studies except Hiep at al. This difference could have arisen from the fact that Hiep T et al may not have included older age children, who in Belgium, the place where they conducted the study may have been seen by adult Nephrologists. Most of the pediatric CKD patients in India seems to be males, as noted by the high sex ratio in our study and the one conducted by Hari et al. This could be because of multiple reasons. Though structural kidney disease is known to be more prevalent in boys, yet gender bias in the society cannot be ruled out.

In our study, anemia was seen in 62.5% which is higher than that found by Wong et al. when 366 children were analyzed was 37%.[16] Baracco R et al showed that iron deficiency was present in 42% of patients of 50 CKD children, out of whom almost half (42.9%) presented with anaemia.[17] Anemia is more prevalent in our study probably due to inadequate micronutrients because of inadequate dietary intake. Further, anemia in CKD due to erythropoietin deficiency may not be adequately treated due to lack of resources. Prevalence of functional iron deficiency in our CKD children is 38.4%, which may further complicate the situation. There are no previous studies to compare with. However, this seems to be a major challenge in treating anemia in these patients.

Hypertension was present in only 27.4% of our patients, in contrast to the study by Wong et al study which showed prevalence of 70%.[16] This difference in prevalence of hypertension in our study could be because we had enrolled more number of patients who were still in stage I CKD. The progression of CKD depends on many factors, one of which is hypertension. Wuhl et al concluded that Hypertension was prevalent in 20 to 80% of children with CKD depending on the degree of renal dysfunction and underlying kidney disease.[18]

In our study, Vitamin D deficiency and insufficiency was seen in 68.9% of CKD patients. Wesseling et al concluded prevalence of Vitamin D deficiency/ insufficiency was 20 to 75% in children with CKD.[19] In a longitudinal study done by Kumar et al in 506 children in the CKiD cohort, vitamin D deficiency (defined as level <20 ng/ml) was observed in 28% of the cohort. The predictor for vitamin D deficiency were age, higher BMI, nonwhite race, season i.e. assessment in the winter, less milk intake, nonuse of nutritional D supplements, and proteinuria.[20] Kuczera et al concluded that as the stage of CKD progress, the prevalence of vitamin D3 increases which was accounting up to 80% in stage 5 CKD. Thus, supplementation is recommended with values< 30 ng/ml.[21] We had a higher incidence of Vitamin D deficiency probably due to non-use of nutritional D supplements, dark skin and less diary product intake, as explained by Kumar et al. Growth failure was found in 54.7% of our cohort whereas Wong study showed prevalence of 12%.[16] For somatic growth and cellular proliferation, appropriate functioning of somatotropic axis is required. This axis, in humans is regulated by several hormones and growth factors (like growth hormones, insulin like growth factor 1, insulin like growth factor 2, IGF binding proteins (IGFBP) and IGFBP protease). In CKD children, the disruption of somatotropic axis has been reported which results in growth retardation. The growth impairment in patient with CKD is associated with increased morbidity and mortality. GH level in CKD is normal or increased because of target organ resistance or insensitivity to growth hormone. In spite of high or normal GH level, rGH is efficacious and safe and results in final catch up of growth in 65% of children.[11] Because significant number of our CKD children are stunted so, timely initiation of rGH could have result in achievement of appropriate target

height. Growth failure was higher in our study population most probably because added complications (anemia, metabolic acidosis was more in our study) which significantly contributes in growth and development of children may not have been addressed in time. In our CKD cohort, 54.8 % of CKD children were stunted and 37.4 % of children were severely stunted.

In our study metabolic acidosis was present in 80 % of our cohort whereas Kraut et al found that metabolic acidosis was present only in 2.3 to 13% of stage 3 CKD and 19% to 37% of stage 4 CKD.[22] The prevalence of metabolic acidosis was more in our population most probably due to late diagnosis and financial constraints in procuring medicines. The consequences of metabolic acidosis are numerous including muscle wasting, bone disease, growth impairment, and abnormalities of growth hormone and thyroid hormone secretion, impaired insulin sensitivity, progression and of renal failure, exacerbation of β2 microglobulin accumulation.[12]

Mineral bone disorder was present in 52.3% of our CKD population studied where as in Wong's study it was present in only 17%.[16] The overall higher prevalence of metabolic acidosis and vitamin D deficiency could have resulted in higher prevalence of mineral bone disorder in our cohort. The incidence of VUR in our study was 17%, PUV was 16% and MCDK13%. In our study, 32.6% were in stage I CKD, 12.1% in stage II CKD; 19.5% in stage III CKD;16.3% in stage IV CKD and 19.5% in stage V CKD. Similarly, Bek K et al. tried to determine the incidence, aetiology and treatment patterns of CKD in children with a questionnaire sent to pediatric nephrology centres in Turkey. The leading causes of CKD were VUR (18.5%), obstructive uropathy (10.7%) and neurogenic bladder (15.1%). The majority of the patients in their study were stage V CKD (32.5%), stage IV CKD (29.8%) or stage III CKD (25.8%)[13] unlike our study. This difference may have occurred as we screen almost all patients visiting Pediatric surgeons with urological problems.[13] Hiep T et al followed 143 successive patients younger than 20 years of age with a glomerular filtration rate of <60 ml/min/1.73 m2 prospectively in Belgium. They found that CAKUT was common seen in almost 58.8% of cases. Out of CAKUT, uropathies were present in 8.4% and VUR were present in 6.3%. Similarly, they had reported nephronophthisis in 4.9% and PCKD in 4.2%. As they enrolled patient with eGFR < 60, 67% were in stage III CKD; 19% were in stage IVCKD and 14% were in stage V CKD.[14] Hari et al. studied a total of 305 children with GFR below 50ml/1.73m2/min. In their study 37.8% had moderate CRF (eGFR =25 to 50); 36.9% had severe CRF (eGFR =10 to 25) and 29.8% had ESRD (eGFR <10). They revealed that commonest cause of CRF were obstructive and reflux nephropathy.[15] Thus, we can conclude that structural kidney diseases seem to be the most common cause of pediatric CKD worldwide. However, anemia, metabolic acidosis, mineral bone disease and growth failure may be more common in our part of the globe. FID may play a significant part in causing anemia in these patients.

6. CONCLUSIONS

Anemia is one of the most common complication seen in CKD patients. As the stage of CKD progresses, the CKD related complications also increases like stunting, hypertension,mineral bone disorder. The prevalence of functional iron deficiency was 38.37%. It is seen in conditions like inflammation, malignancies and infections.We emphasis the need to improve multiple aspects of CKD management, including early diagnosis and treatment of anemia.There are very few studies in adults and almost no study of the same in children with CKD. The mechanism of Functional iron deficiency is yet to be discussed in CKD children.

7. ACKNOWLEDGEMENT: None

8. Conflicts of interest: None

9. REFERENCES

1. Atkinson MA, Furth SL. Anemia in children with chronic kidney disease. Nat Rev Nephrol. 2011; 7(11):635–41.

2. Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, Cavill I, et al. Guideline for the laboratory diagnosis of functional iron deficiency. Br J Haematol. 2013; 161(5):639–48.

3. Kanitkar M. Chronic Kidney Disease in Children: An Indian Perspective. Med J Armed Forces India. 2009; 65(1):45–9.

4. Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. Pediatr Nephrol. 2007; 22(11):1839–48.

5. Organization WH. Nutrition Landscape Information System (NLIS) country profile indicators: interpretation guide. 2010.

6. Prendergast AJ, Humphrey JH. The stunting syndrome in developing countries. Paediatr Int Child Health. 2014; 34(4):250–65.

7. Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al. Recommendations for Blood Pressure Measurement in Humans and Experimental Animals: Part 1: Blood Pressure Measurement in Humans: A Statement for Professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005; 45(1):142–61.

8. Pediatrics AA of. Flynn JT, Kaelber DC, Baker-Smith CM, et al; Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. 2017; 140 (3): e20171904. Pediatrics. 2018; 142(3):e20181739.

9. Taler SJ, Agarwal R, Bakris GL, Flynn JT, Nilsson PM, Rahman M, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD. Am J Kidney Dis. 2013;62(2):201–213.

10. Sinha R. Chronic kidney disease in paediatric population. Clinical Queries: Nephrology. 2013; 2(3):107–15.

11. Roh YE, Kim BR, Choi WB, Kim YM, Cho M-J, Kim H-Y, et al. Vitamin D deficiency in children aged 6 to 12 years: single center's experience in Busan. Ann Pediatr Endocrinol Metab. 2016;21(3):149.

12. Moe SM, Dr eke T, Lameire N, Eknoyan G. Chronic Kidney Disease? Mineral- Bone Disorder: A New Paradigm. Adv Chronic Kidney Dis. 2007;14(1):3–12.

13. Bek K, Akman S, Bilge I, Topalo lu R.kan S, Peru H, et al. Chronic kidney disease in children in Turkey. Pediatr Nephrol. 2009; 24(4):797–806.

14. Mong Hiep TT, Ismaili K, Collart F, Van Damme-Lombaerts R, Godefroid N, Ghuysen M-S, et al. Clinical characteristics and outcomes of children with stage 3-5 chronic kidney disease. Pediatr Nephrol. 2010; 25(5):935–40.

15. Hari P, Singla IK, Mantan M, Kanitkar M, Batra B, Bagga A. Chronic renal failure in children. Indian Pediatr. 2003; 40(11):1035–1042.

16. Wong H, Mylrea K, Feber J, Drukker A, Filler G. Prevalence of complications in children with chronic kidney disease according to KDOQI. Kidney Int. 2006; 70(3):585–590.

17. Baracco R, Saadeh S, Valentini R, Kapur G, Jain A, Mattoo TK. Iron deficiency in children with early chronic kidney disease. Pediatr Nephrol. 2011; 26(11):2077–80.

18. Schaefer F, W ▪l E. Hypertension in Chronic Kidney Disease. In: Flynn JT, Ingelfinger JR, Portman RJ, editors. Pediatric Hypertension. Totowa, NJ: Humana Press; 2013 . 323–42.

19. Wesseling-Perry K, Salusky IB. Phosphate binders, vitamin D and calcimimetics in the management of chronic kidney disease–mineral bone disorders (CKDMBD) in children. Pediatr Nephrol. 2013 Apr;28(4):617–25.

20. Kumar J, McDermott K, Abraham AG, Friedman LA, Johnson VL, Kaskel FJ, et al. Prevalence and correlates of 25-hydroxyvitamin D deficiency in the Chronic Kidney Disease in Children (CKiD) cohort. Pediatr Nephrol. 2016 Jan;31(1):121–9.

21. Kuczera P, Adamczak M, Wiecek A. Endocrine Abnormalities in Patients with Chronic Kidney Disease. PRILOZI. 2015 Dec 1;36 (2):109–18.

22. Kraut JA, Kurtz I. Metabolic Acidosis of CKD: Diagnosis, Clinical Characteristics, and Treatment. Am J Kidney Dis. 2005 Jun;45 (6):978–93.

BIOGRAPHIES

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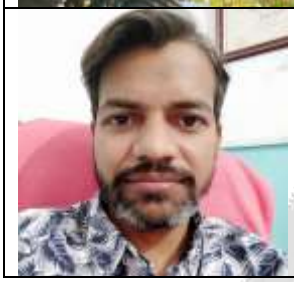	Dr. Rajesh is the Co-author of this study. He is consultant Physician working in Department of Medicine in Bheri Hospital, Nepalgunj, Nepal. He has interest in academics and research. He has several publications to his name. Email id: rkmandal338@gmail.com. Orcid id : https://orcid.org/0000-0002-3099-3731