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ORIGINAL ARTICLE

Correlation of Iron Profile with Different Stages of Chronic Kidney Disease in Children Presenting at a Tertiary Care Hospital

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ABSTRACT

Aim: To determine correlation of iron profile in children with different stages of chronic kidney disease (CKD) presenting to tertiary care hospital.

Methodology: A total of 81 children with chronic kidney disease stage having glomerular filtration rate (GFR) less than 90 (ml/min/m^2) aged 1 – 14 years of either sex were included. Three ml serum sample was taken in vial by hospital duty doctor for serum ferritin level, serum iron, transferrin saturation and total iron binding capacity. The sample was sent to hospital laboratory for reporting. Iron profiling was done evaluating hemoglobin (g/dl), serum iron (ug/dl), serum ferritin (ng/ml), transferrin saturation (%) and total iron binding capacity (ug/dl) while iron load was defined as serum ferritin levels above 300 ng/ml. Correlation of iron profile with different stages of CKD was determined applying one-way analysis of variance (ANOVA).

Results: In a total 81 children, 46 (56.8%) were boys while overall mean age was 7.79±2.30 years. Mean duration on hemodialysis was 11.52 ± 9.97 months. Iron overload was observed in 26 (32.1%) children. Significant association of age above 7 years (p=0.031) and residential status as rural (p=0.017) was noted with iron overload whereas iron overload was increasing with increase in stages of CKD (p=0.002). Hemoglobin levels decreased significantly with increase in stages of CKD (p<0.001). Serum iron levels increased significantly with increase in the CKD stages (p=0.039). Serum ferritin levels were increasing significantly with the increase in CKD stages (p=0.031). Transferrin saturation also increased significant with increase in CKD stages (p=0.027).

Conclusion: High frequency of iron overload was noted in children with CKD on maintenance hemodialysis and there was linear relationship with stages of CKD and iron overload. Significant correlation of hemoglobin, serum iron, serum ferritin and transferrin saturation was observed with different stages of CKD.

Keywords: Iron overload, maintenance hemodialysis, ferritin level.

INTRODUCTION

Chronic kidney disease (CKD) is defined as structural and functional abnormalities of kidney with or without decreasing GFR leading to kidney damage for more than or equal to 3 months with features such as; Abnormalities in composition of blood or urine, abnormalities in imaging test and abnormalities on kidney biopsy.[1] CKD may be caused by congenital, inherited, metabolic or acquired abnormalities[2]. CKD in children <5 year is caused by congenital abnormalities such as hypoplasia, dysplasia or obstructive uropathy, congenital nephrotic syndrome, prune belly syndrome, cortical necrosis, focal segmental necrosis, autosomal recessive polycystic kidney disease, renal vein thrombosis and hemolytic uremic syndrome[3,4]. Acquired causes include various forms of glomerulonephritis and manifested after 5 years of age. Inherited disorders include Familial juvenile nephronophthisis and Alport syndrome while CKD related to metabolic disorders is caused by cystinosis and hyperoxaluria[4]. Main manifestations of CKD include growth failure, metabolic acidosis, anemia, mineral bone disease and hypertension[5]. Regular packed red cells transfusions eliminate the complications of anemia and compensatory bone marrow expansion[3]. Repeated transfusion deposit the iron in body as one unit of blood contains about 200mg iron (PCV 1ml=0.7mg iron, whole blood 1ml=0.35mg iron)[2,3]. Saturated iron with transferrin is non-toxic to tissues. When 60-70% transferrin saturation is achieved, free iron called non-transferrin bound iron (NTBI) is taken by tissues, which is highly toxic due to free radical formation[3,6].

Iron overload can lead to serious morbidities including cardiac disease, cirrhosis, diabetes, hypothyroidism and hyperparathyroidism. Iron chelation therapy is used to decrease the morbidity and mortality in chronic kidney disease patients[7]. Available iron chelators are Desferrioxamine (IV), Deferiprone (Oral) and Deferasirox (Oral)[5]. Desferrioxamine has been used as the first line drug for chelation uptil now. It is a parenteral drug used 5-6 times a week for effective iron chelation.[8] Because of parenteral route of administration, the compliance is poor. Deferiprone is an oral iron chelator given three times daily whereas Deferasirox is claimed to be a promising new oral iron chelator used in once daily dosage[8]. Its efficacy is said to be similar to that of Desferrioxamine[9,10]. In a study on hemodialysis done at Sudanese patients in 2017 by Khidher ibrahim, it was found that mean serum ferritin in hemodialysis patients was 521.8[11]. In another study conducted in France by Department of Medical Technology

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in 2016 showed that severe iron overload was present in 30.2% of patients[12].

Previously limited work has been done on this subject in Pakistan, most of the studies have been conducted on adult population. It is important to identify patients with iron overload in order to identify distinctive treatment. The Children's hospital and the institute of child health Multan, Pakistan is the only regional center in south Punjab for the management of chronic kidney disease on hemodialysis, where 500-600 patients are managed every year. No local data is available. Therefore present study is planned so that early treatment can lead to good prognosis. This study was done to determine correlation of iron profile in children with different stages of chronic kidney disease presenting to tertiary care hospital.

METHODOLOGY

This descriptive cross sectional study was done at Department of pediatric Nephrology Children's Hospital & the Institute of Child Health, Multan from 1st June 2020 to 30th November 2020. A total of 81 children with chronic kidney disease stage 2-5 having GFR less than 90 (ml/min/m^2) aged 1–14 years of either sex were included in our study while patients with chronic liver disease, cardiovascular disorders, bleeding disorders and congenital anomalies were excluded. Sample size was 81 children with chronic kidney disease, sample size was calculated using Epi–Info software for single proportion sample size calculator using; P=Expected prevalence =30.2%[11], confidence level =1-α=95%= .96, and absolute precision required = d= 0.1(10%).

Study was started after taking permission from the institutional ethical committee. Those patients, who fulfill the inclusion and exclusion criteria, were recruited for the study. After explaining risks and benefits of the study, written informed consent was taken from the parents/guardians. In diagnosed patients of chronic kidney disease stage 2 – 5, 3ml serum sample was taken in vial by hospital duty doctor for serum ferritin level, serum iron, transferrin saturation, total iron binding capacity. The sample was sent to hospital laboratory for reporting. Iron profiling was done evaluating hemoglobin (g/dl), serum iron (ug/dl), serum ferritin (ng/ml), transferrin saturation (%) and total iron binding capacity (ug/dl) while iron load was defined as serum ferritin levels above 300 ng/ml.

Data was entered in SPSS version 23.0. Descriptive statistics was applied to analyze the data. The quantitative variables like age, weight, duration of disease were calculated as mean and standard deviation. The outcome variable (iron overload) and gender were calculated in frequencies and percentages. Confounding factors like age, weight, gender and duration of disease was controlled by stratification and chi-square test was applied to see effect of these on outcome. One-way Analysis of variance (ANOVA) was applied to note any significant correlation between different iron parameters and CKD stages. P≤0.05 was taken as significant.

RESULTS

Our study included 81 children with chronic kidney disease including 46(56.8%) boys versus 35(43.2%) were girls having mean age 7.79±2.30 years (range 3–12 years) and 44(54.3%) were aged more than 7 years. Of these 81 patients, 43(53.1%) belonged to rural areas. Poor socioeconomic status was noted in 44(54.3%) children. Mean weight was noted to be 22.12±6.63 kilograms and 41(50.6%) children had weight more than 20 kilograms. Chronic kidney disease (CKD) stage 2 was noted in 10(12.3%), stage 3 CKD in 31(38.3%), stage 4 CKD in 23(28.4%) and 17(21%) presented with stage 5 CKD on hemodialysis while mean duration on hemodialysis was 11.52 ± 9.97 months. Iron overload was observed in 26 (32.1%) children. Table 1 is showing stratification of iron overload with regards to study variables. Significant association of age above 7 years (p=0.031) and residential status as rural (p=0.017) was noted with iron overload. Table 1 is also showing that iron overload was increasing with increase in stages of CKD (p=0.002).

Overall, mean hemoglobin, serum ferritin and transferrin saturation were calculated to be 11.8±2.6 mg/dl, 158±112ng/ml and 32±16%. Table 2 is estimating correlations of hemoglobin (g/dl), serum iron (ug/dl), serum ferritin (ng/ml), transferrin saturation (%) and TIBC with different stages of CKD. Hemoglobin levels decreased significantly with increase in stages of CKD (p<0.001). Serum iron levels increased significantly with increase in the CKD stages (p=0.039). Serum ferritin levels were increasing significantly with the increase in CKD stages (p=0.031). Transferrin saturation also increased significant with increase in CKD stages (p=0.027).

Table 1: Stratification of iron overload with regards to study variables (n=81)

Study Variables	Iron overload		P value
	Yes	No	
Gender			
Male (n= 46)	15	31	**0.999**
Female (n=35)	11	24	
Age groups			
Up to 7 Years (n= 37)	07	30	**0.031**
More than 7 Years (n=44)	19	25	
Residential status			
Rural (n= 43)	19	24	**0.017**
Urban (n=38)	07	31	
Socioeconomic status			
Poor (n=44)	14	30	**0.999**
Middle Income (n=37)	12	25	
Weight			
Up to 20 Kilograms (n=40)	11	29	**0.477**
More than 20 Kilograms (n=41)	15	26	
Stages of CKD			
Stage 2 (n=10)	02	08	**0.002**
Stage 3 (n=31)	02	29	
Stage 4 (n=23)	07	16	
Stage 5 (n=17)	15	02	
Duration on hemodialysis (n=17)			
Up to 12 months (n=04)	02	02	**0.025**
More than 12 months (n=13)	12	00	

Table 2: Association of Hemoglobin, Serum Ferritin and Transferrin Saturation with Different Stages of Chronic Kidney Disease (n=81)

Parameters	Stages of CKD				P-Value*
	2 (n=10)	3 (n=31)	4 (n=23)	5 (n=17)	
Hemoglobin (g/dl)	12.9±1.8	12.2±1.6	10.6±2.1	9.4±2.8	<0.001
Serum Iron (ug/dl)	82.5±56.2	94.6±80.4	114.3±92.8	168.7±118.2	0.039
Serum Ferritin (ng/ml)	91.5±86.2	128.6±91.2	178.8±236.2	269.3±224.2	0.031
Transferrin Saturation (%)	23±14	30±20	38±34	53±38	0.027
TIBC (ug/dl)	341.1±224.8	271.5±188.4	311.8±197.0	303.2±267.6	0.804

*Correlation calculated using One-Way ANOVA

DISCUSSION

Among healthy human subjects, iron store is estimated to rage 800 mg to 1200 mg, although some studies have also suggested up to 1500 mg. Iron in our bodies is stored in ferritin which can be later utilized by our body and ferritin level is directly proportional to the amount of iron stored in our body[13-14]. In children on dialysis, anemia is common presentation so regular blood transfusions and recombinant human erythropoietin therapy are routinely employed to overcome anemia.[15] These therapies are associated with further complications such as iron overload, deposition of iron in reticular endothelial system, shortness of breath, enlargement of spleen, arthritis and liver diseases[16].

Our study included 81 children with CKD while there were 56.8% boys versus 43.2% girls. Different studies have shown male gender predominance in CKD pediatric population. A study conducted by Shuaib et al[17] has also reported 66.7% boys with CKD, similar to our findings. Shakir et al[18] has also reported 60.8% male gender predominance. Jaramillo et al[19] from Mexico has also reported similar results. Ambarsarri et al[20] from Indonesia has also reported 71.4% boys on hemodialysis which is again showing high trends of male gender predominance.

Mean age of our patients was 7.79±2.30 years (range 3–12 years) and 54.3% were aged more than 7 years. A study conducted by Shuaib et al[17] reported 11.31±2.63 years mean age of the children with CKD. Shakir et al[18] revealed 9.92±2.60 years mean age, close to our results. Jaramillo et al[19] from Mexico has reported 13 years median age which is slightly higher than our mean ages, the reason for this difference is due to their inclusion criteria as they included patients up to 17 years of age and our inclusion criteria ranged 1–14 years old patients only. Ambarsarri et al[20] from Indonesia has also reported 13.5 years mean age and difference is due to the same reasons as was for Jaramillo et al.[19]

Of these 81 patients, 53.1 % (n = 43) belonged to rural areas while 46.9 % (n = 38) were from urban localities. Poor socioeconomic status was noted in 54.3 % (n=44) while 45.7 % (n=370 were having middle income social status. A study conducted by Shuaib et al [17] has also reported 54.97 % children on hemodialysis were from rural areas, similar to that of our results.

Mean weight was noted to be 22.12 ± 6.63 kilograms and 50.6% cases had weight more than 20 kilograms. A study conducted by Shuaib et al[17] has also reported 24.97±15.88 kilograms mean weight of the children undergoing hemodialysis. Shakir et al[18] has also reported 19.65± 4.71 kilograms mean weight, similar to our results. Jaramillo et al[19] from Mexico has also reported similar results.

In the present study, CKD stage 2 was noted in 12.3%, stage 3 CKD in 38.3%, stage 4 CKD in 28.4% and 21% presented with stage 5 CKD on hemodialysis while mean duration on hemodialysis was 11.52±9.97 months. A study conducted by Shuaib et al[17] has also reported 11.91±7.06 months mean duration on hemodialysis, close to our study results. Shakir et al[18] has also reported similar results. Jaramillo et al[19] from Mexico has also reported similar results.

In this study, iron overload was noted in 32.1% children. Jaramillo et al[19] from Mexico has also reported 28.3% iron overload in hemodialysis patients, close to our results. Ambarsarri et al[20] from Indonesia has also reported 29% children with iron overload. Serum iron overload was more prevalent in children with increasing age (p=0.031), similar results have been reported by Jaramillo et al [19] and this high prevalence of iron overload in older pediatric population can be due to prolonged duration of illness and therapy in this population subset. Similarly iron overload was also more prevalent in children who belonged to rural areas due to poor compliance with the treatment in these patients due to lack of health education and facilities in our rural areas. Prolonged duration on hemodialysis was also predictor for iron overload, similar results have been reported by Jaramillo et al[19].

We noted that hemoglobin levels decreased significantly with increase in stages of CKD (p<0.001) while serum ferritin levels were increasing significantly with the increase in CKD stages (p=0.031). Our findings were quite similar to what has been reported by Lee KH et al in Know-Ped CKD study for Korea. It is really important to understand various factors causing iron overload and anemia in various stages of CKD and this will improve outcome in these children. No single laboratory measure can estimate the extent of iron deficiency so evaluation of iron stores in terms of serum iron, serum ferritin and transferrin levels is vital.

Our study had some limitations as well. As this was a single center study with a relatively small sample size, our findings cannot be generalized. We were unable to estimate the role of diets and calorie intake in our cohort. We did not note influence of different treatment regimens and outcome of children with CKD in the present study. More studies should be conducted to evaluate relationship of iron overload and variation in different iron parameters in different stages of CKD so customized treatment plans can be recommended for these set of children.

CONCLUSION

High frequency of iron overload was noted in children with CKD on maintenance hemodialysis and there was linear relationship with stages of CKD and iron overload.

Significant correlation of hemoglobin, serum iron, serum ferritin and transferrin saturation was observed with different stages of CKD.

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