

Original Article**Role of Serum Heparin Level in Predicting Anemia and Cardiovascular Morbidity in Children with Chronic Kidney Disease.**

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Abstract

Introduction: The risk of mortality for pediatric patients with severe chronic kidney disease (CKD) is 30-fold higher than that for healthy patients of the same age. The main cause of death is cardiovascular disease (CVD), accounting for 25–50 % of deaths in children and young adults with childhood onset CKD.

Aim of the study: To study serum heparin level and its role in anemia and cardiovascular dysfunction in children with CKD, either on hemodialysis (HD) or on conservative therapy.

Methods: Serum samples were obtained from 20 healthy individuals and from 30 patients with CKD on regular dialysis (group I) and 20 patients with chronic kidney diseases on conservative therapy (group II). The levels of hemoglobin, serum ferritin, s. iron, TIBC, serum heparin, and echo parameters in form of fractional shortening (FS), left ventricular mass index (LVMI) and trans mitral to mitral annular early diastolic velocity ratio (E/Ea') ratio were determined and the correlation between them was studied.

Results: There is a significant increase in the serum heparin levels in group I and group II than the control group. There was significant correlation between heparin and serum ferritin, s. iron, transferrin saturation, FS, LVMI, E/Ea' while there was a negative correlation between serum heparin and both hemoglobin and TIBC.

Conclusion: Heparin level is a good biomarker for anemia and cardiac dysfunction in patients with chronic kidney disease.

Keywords: anemia, chronic renal failure, heparin, cardiovascular dysfunction

Running title: Role of Serum Heparin Level in Predicting Anemia and Cardiovascular Morbidity in Children with Chronic Kidney Disease.

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geget : The Journal of the Egyptian Society of Pediatric Nephrology and Transplantation (ESPNT)

geget <https://geget.journals.ekb.eg/>

Published by ESPNT <http://espnt.net/>

Cohosted by Egyptian Knowledge Bank <https://www.ekb.eg>

INTRODUCTION

The risk of mortality for pediatric patients with severe chronic kidney disease (CKD) is 30-fold higher than that for healthy patients of the same age [1]. Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in children and adults with end-stage renal disease (ESRD). In children with ESRD, mortality is attributed to CVD in 23% of children in the United States and up to 50% in other countries [2].

Researchers have described three pathological forms of CVD prevalent in patients with CKD. The first one is atherosclerosis which is considered as the primary etiology of ischemic heart disease (IHD) in that subset of patients. [3]. The second pathology is an alteration in heart geometry. It includes left ventricular (LV) remodeling, concentric LV hypertrophy (LVH), and eccentric LVH. [4]. The third pathological form is arteriosclerosis – a large vessel disease. This process involves loss of elasticity, vessel remodeling, and development of non-compliant arteries [5].

A low hemoglobin level is a common comorbidity in children with CKD and is associated with multiple adverse clinical consequences, including mortality and the development and progression of cardiovascular risk factors, such as left ventricular hypertrophy (LVH) [6]. The main cause of anemia in CKD is the decreased production of erythropoietin which is in line with the degree of impairment of renal function. Treatment with erythropoietin stimulating agents (ESA) could increase Hb level and improve cardiovascular function of most CKD patients, thus improving the prognosis of

CKD [7]. However, some patients were hypo or non-responsive, as shown by the low level of Hb in more than 20% of children with advanced CKD despite administration of ESA [8].

Iron deficiency anemia is a common complication of chronic kidney disease (CKD) [9]. This is due to both true paucity of iron stores (absolute IDA) and relative (functional) iron deficiency; the latter being due to underlying inflammation which impairs the body's ability to appropriately utilize the iron sequestered in the tissues. The identification of hepcidin as a key iron-regulatory protein has helped to clarify the mechanisms underlying the anemia of chronic kidney disease (CKD), beyond erythropoietin deficiency alone [10]. Hepcidin, a peptide hormone produced by hepatocytes, is the central regulator of systemic iron homeostasis through its interaction with ferroportin, the major cellular iron export protein. Hepcidin binding to ferroportin results in reduced iron export from macrophages and intestinal absorptive cells, leading to decreased serum iron levels [11].

Increased iron, inflammation leads to increase in hepcidin; however, hypoxia, anemia, and decrease in iron stores leads to decrease in hepcidin. Hepcidin is the main iron regulatory hormone. Once secreted into the circulation, hepcidin binds to ferroportin (iron transporter) on enterocytes and macrophages, which trigger its internalization and lysosomal degradation. Thus, in chronic inflammation, the excess of hepcidin decreases iron absorption and prevents iron recycling, which results in hypoferritinemia and iron restricted erythropoiesis, despite normal iron stores (functional ID), and anemia of chronic

disease, which can evolve to anemia of chronic disease plus true ID. In contrast, low hepcidin expression may lead to iron overload, and vice-versa [12].

The potential relationship between cardiac status and EPO resistance in CKD patients should be explored. However, there are no universal definitions or markers for EPO resistance in CKD patients. Serum hepcidin, an iron sequestering peptide, has been suggested to be fundamental for EPO resistance [13].

Therefore, we performed the current study to identify the relationship between anemia and hepcidin and to correlate cardiac function and geometry with serum hepcidin levels in CKD patients either on dialysis or conservative therapy.

METHODS

The present study was carried out in the Department of Pediatrics in Benha University Hospital, during the period from March 2020 to September 2021, after getting acceptance from the ethical committee of the Faculty of Medicine and getting written consents from patients.

The present study was carried out on 70 children divided into three groups: Group I included 30 patients with ESRD of different causes on regular HD therapy three times/week, with each dialysis session lasting for 3–4 h. They were 15 boys and 15 girls. Their ages ranged from 5 to 16 years. They have been free from acute dialysis-related complications for at least 30 days before recruitment. Dialysis was started when GFR was equal or less than 15 ml/min/1.73 m². Group II included 20 patients with CKD of different causes on conservative

therapy (stages 2–4 CKD) who did not require dialysis before. They were 9 boys and 11 girls. Their ages ranged from 4 to 16 years.

Group III included 20 apparently healthy children with age and sex matched were chosen as control group.

All patients received (before and during the study) supportive therapy in the form of subcutaneous EPO in a dose of 50 IU/kg/setting, intravenous iron dextran 100 mg/week, oral folic acid 1 mg/day, oral calcium 1000 mg/day, oral vitamin D (1 α) in a dose of 0.01–0.05 μ g/kg/day, and oral antihypertensive medications for hypertensive patients.

Exclusion criteria: The following patients were excluded from this study.

- 1) Patients previously diagnosed with non-renal cause of anemia other than iron deficiency.
- 2) Patients with evidence of active or occult bleeding.
- 3) Blood transfusion within the past 4 months.
- 4) History of malignancy, end-stage liver disease, or chronic hypoxia.
- 5) Recent hospitalization or infection requiring antibiotics within the past 4 weeks.

Patients were dialyzed on Fresenius 4008B and 5008s dialysis machine (Bad Homburg, Germany) at blood flow rate = $2.5 \times \text{weight (kg)} + 100$ ml/min, using polysulfone hollow fiber dialyzers suitable for the surface area of the patients (Fresenius F3 = 0.4 m², F4 = 0.7 m², F5 = 1.0 m², and F6 = 1.2 m²). Bicarbonate dialysis solutions were used. All investigations were carried out before starting the HD session.

All patients and controls were subjected to the following:

- 1) Full history taking: including age, sex, residence, socioeconomic status, full nutritional history, duration of dialysis, and regular drug taking doses.
- 2) Clinical examination:
 - a. Anthropometric measures including weight and height
 - b. Systemic examination including chest, heart, abdominal, and neurological examination.
 - c. Laboratory investigations: routine investigations including complete blood count, serum iron, TIBC, ferritin level, blood urea, serum creatinine, Na, K, Ca, Ph, PTH.
 - d. Specific investigations:
 - Quantitative measurement of bioactive hepcidin in serum was carried out using enzyme-linked immunosorbent assay (ELISA) [14]. For children in group I, hepcidin was carried out before the dialysis setting.
 - ECHO was done by an experienced echo cardiologist in the cardiology unit of Benha University Hospital for Children.

Two dimensional guided M mode echocardiography was performed by standard methods.

- Fractional shortening (FS) for systolic function.
- Transmitral to mitral annular early diastolic velocity ratio using tissue Doppler for diastolic dysfunction (E/Ea’).
- Left ventricular internal dimension and interventricular septal and posterior wall thickness were measured at end-diastole and end-systole, according to the American Society of Echocardiography guidelines. LVH was determined as LVMI.

LVMI was calculated using the anatomically validated formula: LVM

was calculated at end diastole by using the American Society of Echocardiography convention [4]: $LV\ mass = 0.8 (1.04 ([LVVIDD+PWTD+IVSTD] 3-[LVVIDD])) +0.6g$, Where LVVIDD is the left ventricular internal diameter in diastole, PWTD is the posterior wall thickness in diastole, and IVSTD is the interventricular septal thickness in diastole. LVMI was measured as follow: $LVMI = LVM/body\ surface\ area$.

Statistical analysis

Data were analyzed using SPSS software, version 22.0 (IBM, Armonk, NY, USA) for Windows. Categorical data were presented as number and percentages, Chi square (χ^2) and Fisher’s exact tests were used to analyze them. Quantitative data were tested for normality using Shapiro-Wilks test assuming normality at $P>0.05$. Normally distributed variables were expressed as mean \pm standard deviation and analyzed by Student “t” test and ANOVA for 2 and 3 independent groups respectively, while non parametric ones were presented as median and inter-quartile range (IQR), and analyzed by Mann Whitney U test or Kruskal Wallis (KW) test for 2 independent groups or more respectively.

Significant ANOVA or KW was followed by post hoc multiple comparisons using Bonferroni adjusted tests to detect the significant pairs. Linear association between variables was assessed by Spearman’s correlation coefficients for non-parametric variables.

ROC curve was constructed to assess the validity and predictivity of hepcidin level in detection of cardiac dysfunction and anemia among CKD patients. $P \leq 0.05$ was considered significant. P value >0.05 is non-significant (NS), $P < 0.05$ is

significant (S), $P \leq 0.001$ is highly significant (HS).

RESULTS

The present study was conducted on 70 children who were divided into three groups. Group I included 30 patients with ESRD under HD therapy.

Group II included 20 patients with CKD under conservative treatment.

Group III included 20 apparently healthy children as control group.

There was no significant difference between age and sex in the studied groups. The causes of CRF of the patients in group I and group II obstructive uropathy in nineteen patients (38%), cystic kidney disease in four patients (8%), Focal segmental sclerosis in six patients (12%), hyperoxaluria in two patients (4%), Systemic lupus erythematosus in three patients (6%), hemolytic Uremic syndrome in 3 patients (6%), renal vasculitis in one patient (2%) and the remaining twelve patients (24%) were chronic kidney disease of unknown etiology.

There was a significant decrease in body weight and height of the patient groups compared with controls ($P < 0.05$). There was a highly significant increase in blood pressure in group I and II than group III. There was a highly significant decrease in Hb of group I and group II than in group III ($P < 0.05$) while there was significant increase in the serum iron, TIBC in group I and group II as compared with the control group III (p value 0.009 and 0.004) (Table 1). There was a highly significant increase in serum ferritin levels in group I and group II as compared with the control group III ($P < 0.001$) (Table 1). There was a highly significant

increase in the serum parathyroid hormone in group I and group II as compared with group III ($P < 0.001$).

There was a highly significant increase in serum hepcidin in group I and II than group III (P value 0.001). Hepcidin was higher in dialysis group than conservative group (Table 2).

There is statistically significant increase in FS and E/Ea' ratio I group I and group II than group III (P value 0.002). There is a highly significant increase in LVMI in group I and group II than group III (P value < 0.001) (Table 3).

There was significant increase in serum hepcidin in anemic than non-anemic group (p value 0.006) (Table 4). The best cut-off level of serum hepcidin was 158.5 ng/ml with AUC was 0.741 with sensitivity 78.8% and specificity 52.9% for detection of anemia. (Table 5).

Cardiac dysfunction was present in 63.3% of dialysis patients and 30% of conservative group with statistically significant difference (p value 0.021). There was significant increase in serum hepcidin in patient with cardiac dysfunction than non-cardiac patients (p value 0.004) (Table 6). The best cut-off level of serum hepcidin was 278 ng/ml with AUC was .736 with sensitivity 68% and specificity 72% for detection of anemia (Table 7).

There was a significant negative correlation between serum hepcidin and Hb level both in group I and II (Figure 1). There is high significant positive correlation between serum hepcidin and serum iron (Figure 2), Transferrin saturation (Figure 3) and ferritin (Figure 4).

On studying Echo parameters with correlation with serum hepcidin we found

that FS, E/Ea' (Figure 5) ratio and LVMI (Figure 6) were strongly positively correlated with serum hepcidin. There

was statistically significant +ve correlation between anemia and cardiac dysfunction.

Table 1: Hemoglobin and iron profile among the studied groups

Variables	Dialysis group (n=30)		Conservative Group (no = 20)		Control group (no 20)		ANOVA	P value
	Mean	± SD	Mean	± SD	Mean	± SD		
Hb (g/dl)	9.6*	2.43	10.7*	2.24	13.2	0.65	19.5	<0.001 (HS)
Transferrin saturation (%)	31.1†	12.09	22.9	8.36	24.8	5.85	5.07	0.009 (S)
Serum iron (ug/dl)	115.7*†	37.1	93.4	32.1	87.2	14.3	6.04	0.004 (S)
TIBC (ug/dl)	387.3*	55.5	406.6*	32.3	333.0	44.3	13.5	<0.001 (HS)
	Median	IQR	Median	IQR	Median	IQR	KW	
Serum ferritin (ng/ml)	832.5*†	486.7-1264	93.0	40.7-347.5	72.0	58.5-90.7	34.1	<0.001 (HS)

*Significant compared to controls, †Sig compared to conservative group, KW=Kruskal Wallis test, S= significant, HS = highly significant

Table 2: Serum hepcidin level among the studied groups

Variables	Dialysis group (n=30)		Conservative group (n=20)		Control group (n=20)		KW test	P Value
	Median	IQR	Median	IQR	Median	IQR		
Serum Hepcidin (ng/ml)	534.0*†	337.5-650	127.5*	57-189.8	29	20.3-40.8	48.3	<0.001 (HS)

Table 3: Echo findings among the studied groups

Variables	Dialysis group (n=30)		Conservative group (n=20)		Control group		ANOVA	P value
	Mean	±SD	Mean	±SD	Mean	±SD		
FS	35.2*	5.5	32.5	4.9	30.4	1.63	6.8	0.002 (S)
E/Ea ratio	14	0.57	10	0.27	8	0.28	4.22	0.019 (S)
LVMI (gm/m2)	123.1*	66.6	97.2*	60.2	48.0	11.4	11.4	<0.001 (HS)

FS = fractional shortening, E/Ea = transmitral to mitral annular early diastolic velocity ratio

LVMI = left ventricular mass index, *Significant compared to controls

Table 4: Level of hepcidin among anemic group patients of chronic kidney disease

Variables	No anemia (n=17)		Anemia (n=33)		ZMWU	P value
	Median	IQR	Median	IQR		
Serum Hepcidin (ng/ml)	152.0	38.5-357.5	469.0	198-584	2.76	0.006 (S)

Table 5: Sensitivity & specificity of serum Hepcidin for detection of anemia in chronic kidney disease patients

Variable	Sens %	Spec %	PPV%	NPV%	AUC	95%CI	P Value
Hepcidin ≥158.5(ng/ml)	78.8%	52.9%	74.5%	56.3%	0.741	0.6-0.88	0.006 (S)

Table 6: Level of hepcidin according to cardiac dysfunction in CKD patients

Variables	No cardiac dysfunction (n=25)		Cardiac dysfunction (n=25)		ZMWU	P value
	Median	IQR	Median	IQR		
Serum Hepcidin (ng/ml)	198.0	116-362	487.0	239-594	2.86	0.004 (S)

Table 7: Sensitivity and specificity of serum Hepcidin for detection of cardiac dysfunction in chronic kidney disease patients

Variable	Sens %	Spec %	PPV%	NPV%	AUC	95%CI	P Value
Hepcidin ≥278 (ng/ml)	68%	72%	70.8%	69.2%	0.736	0.6-0.87	0.004 (S)

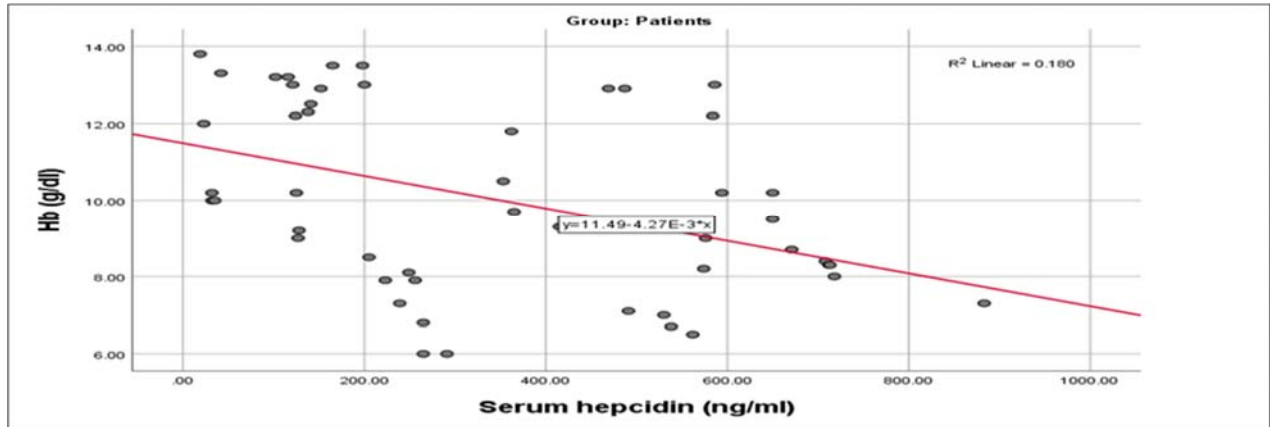


Figure 1 : Scatter graph showing significant negative correlation between serum hepcidin and Hb.

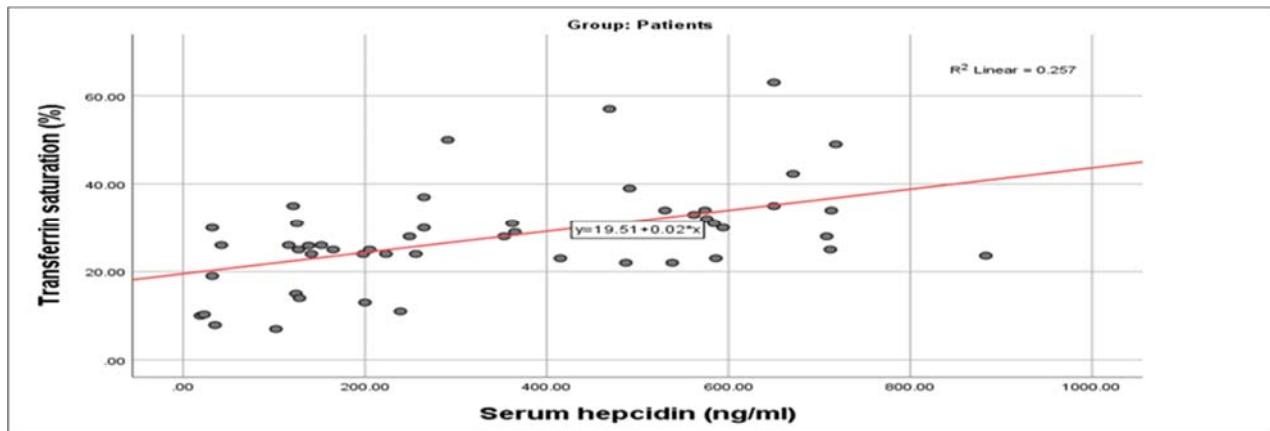


Figure 2: Scatter graph showing significant positive correlation between serum hepcidin and serum iron.

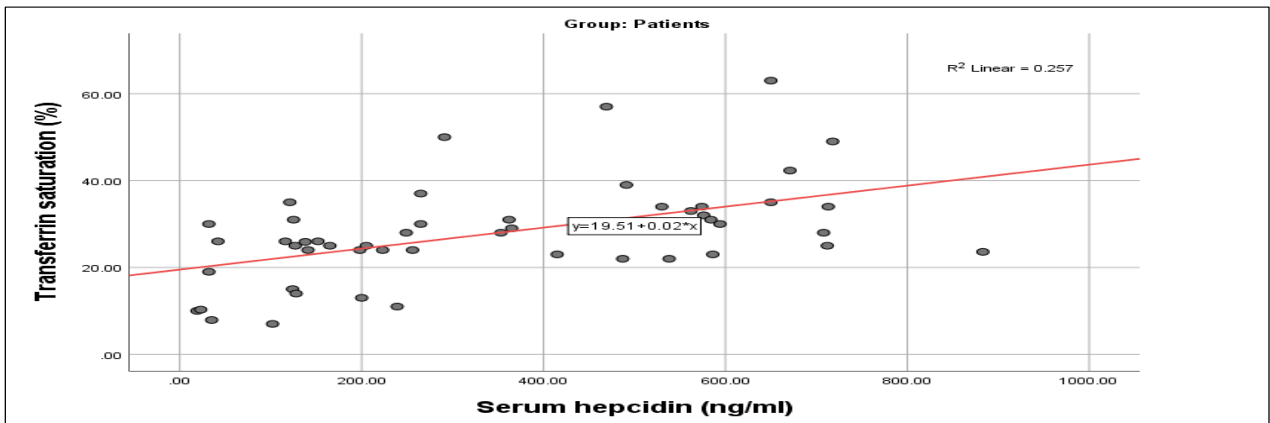


Figure 3 : Scatter graph showing significant positive correlation between serum hepcidin and transferrin saturation.

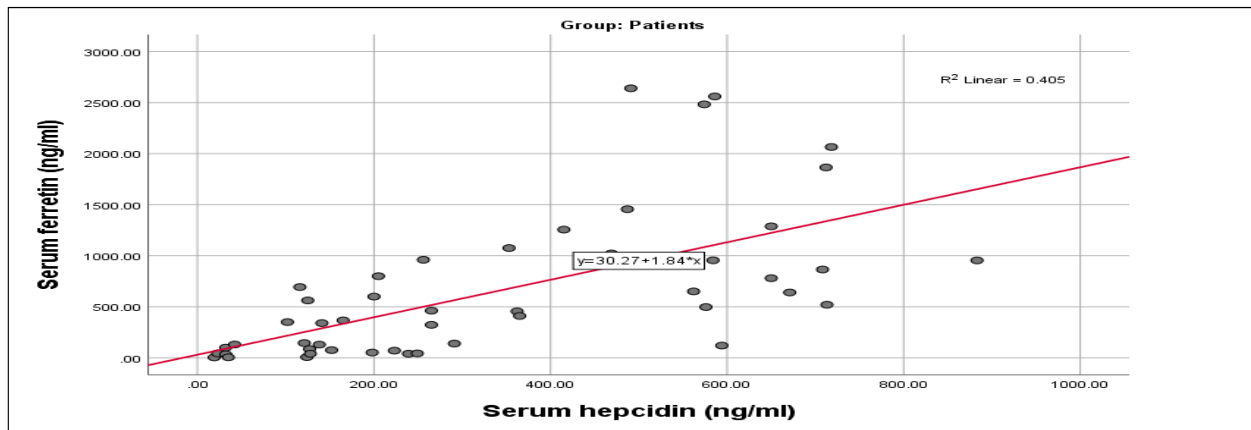


Figure 4: Scatter graph showing significant positive correlation between serum hepcidin and Hemoglobin.

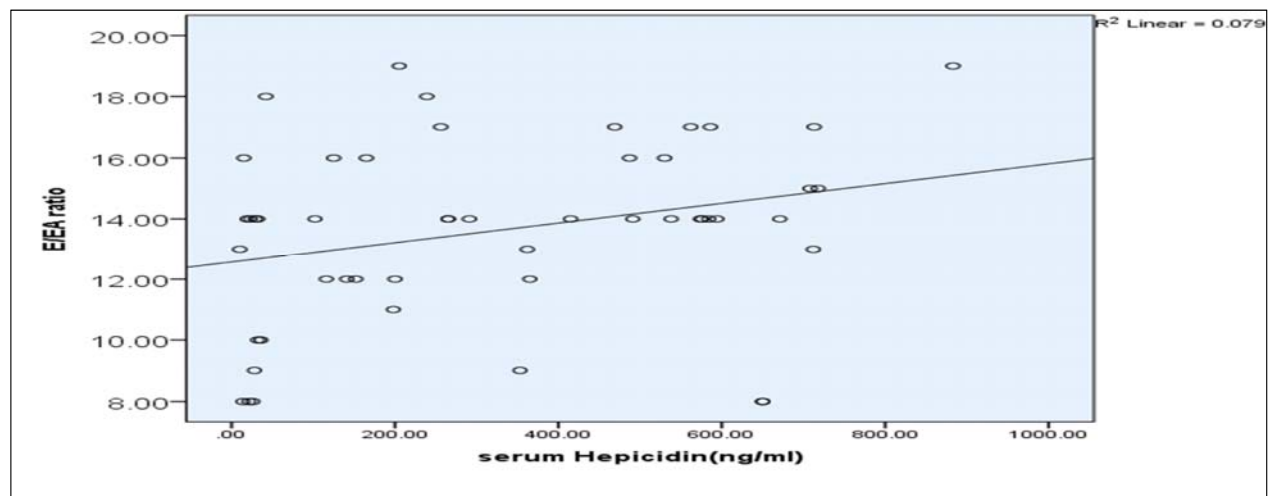


Figure 5: Scatter graph showing significant positive correlation between serum hepcidin and E/Ea' ratio.

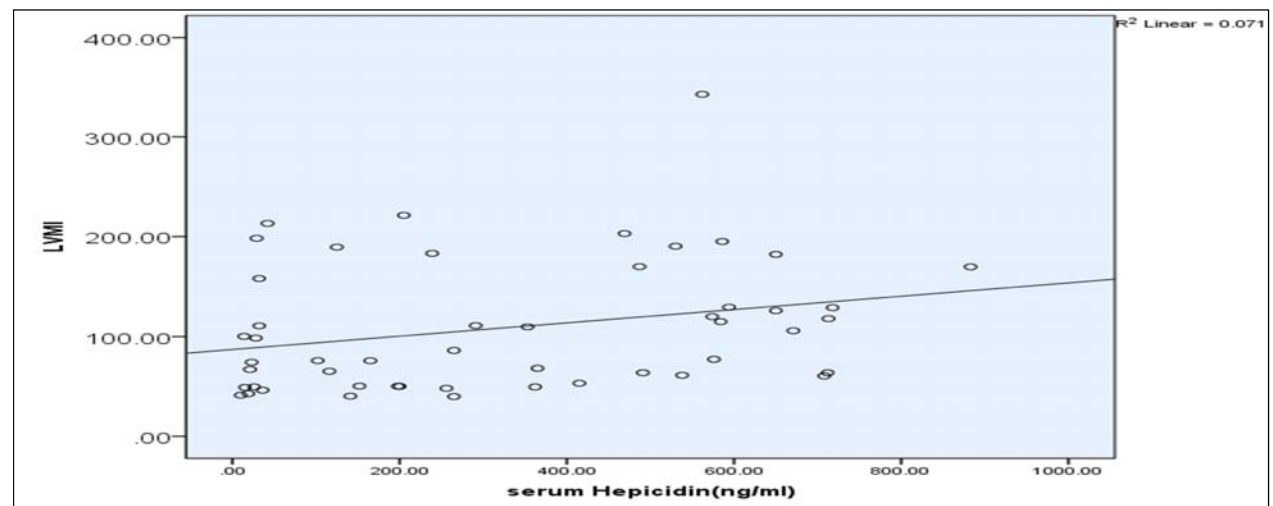


Figure 6 : Scatter graph showing significant positive correlation between serum hepcidin and Left ventricular mass index.

DISCUSSION

The risk of mortality for pediatric patients with severe chronic kidney disease (CKD) is 30-fold higher than that for healthy patients of the same age [1]. The main cause of death is cardiovascular disease (CVD), accounting for 25–50 % of deaths in children and young adults with childhood onset CKD [2].

Anemia is a frequent and serious complication of CKD and a risk factor for early death. Anemia conveys significant risk for cardiovascular disease, faster progression of renal failure, and decreased quality of life. Patients with CKD can have anemia for many reasons, with the severity being proportional to the degree of renal insufficiency. Anemia develops when the creatinine clearance has decreased to 30–40 ml/min/1.73 m² [15].

The potential relationship between cardiac status and EPO resistance in CKD patients should be explored. However, there are no universal definitions or markers for EPO resistance in CKD patients. Serum hepcidin, an iron sequestering peptide, has been recently suggested to be fundamental for EPO resistance.

The present study was conducted to evaluate serum hepcidin level (using a ELISA assay) in pediatric patients with ESRD under regular HD therapy and patients with CKD under conservative treatment, and its possible role in the pathogenesis of anemia in those patients and the relationship between serum hepcidin and cardiac status in pediatric CKD patients.

The present study showed high statistically significant difference

regarding hemoglobin between the diseased groups and control group as the mean Hb is 9.6 and 10.7 in group I and group II and 13.2 in the control group.

The introduction of ESAs, such as EPO, has allowed effective treatment of anemia in patients with CKD. However, rhEPO resistance often associated with iron deficiency and inflammation remains a challenging problem [16].

Hepcidin is a key regulator of iron homeostasis and plays a role in the pathogenesis of anemia of chronic disease. Its levels are increased in patients with chronic kidney disease (CKD) due to diminished renal clearance and an inflammatory state. Increased hepcidin levels in CKD patients are supposed to be responsible for functional iron deficiency in these patients and contribute to renal anemia and resistance to erythropoiesis-stimulating agents [17].

In our study, serum hepcidin showed high statistically significant difference among studied groups regarding hepcidin level as it was higher in dialysis group and conservative group than control group (p value <0.001). Also there is high statistically significant difference between dialysis group and conservative group with mean 534 and 127 ng/ml respectively.

Our study is in agreement with Ali et al. [18] who studied Serum hepcidin level in children with chronic kidney disease either on hemodialysis or on conservative therapy on 3 groups: 20 patients on hemodialysis, 10 patients on conservative therapy and 30 healthy control group. They found that Serum hepcidin level in children with CKD either on hemodialysis or on conservative therapy with mean 213 and 118 ng/ml

respectively. Zabriskie et al. [19] also measured serum hepcidin in 26 pediatric HD patients and found elevated serum hepcidin level median (652.4 ng/ml) that is close to our study (534ng/ml).

In our present study, there was high statistically significant positive correlation between serum hepcidin and serum iron, transferrin saturation and ferritin (p value was 0.001) while there was statistically significant negative correlation with TIBC (p value 0.016).

Kamal et al. [20] also studied hepcidin level in patients with chronic kidney disease and its correlation with markers of iron status in Zagazig University Hospital found that Serum level of hepcidin was increase by worsening the stages of CKD, and more increase in regular HD patients. There was high statistically significant positive correlation of hepcidin level with serum ferritin ($P<0.001$), serum iron ($P<0.05$) in CKD and negative correlation with Hb, eGFR ($P<0.001$), and it was not correlated with total iron binding capacity (TIBC) ($P<0.48$).

Zaritsky et al. [19] who studied Hpcidin as a potential novel biomarker for iron status in chronic kidney disease on n 48 pediatric (PCKD2-4) and 32 adults (ACKD2-4) patients with stages 2 to 4 CKD along with 26 pediatric patients with stage 5 CKD (PCKD5D) on peritoneal dialysis also found that hepcidin was significantly increased in PCKD2-4 (127.3 ng/ml), ACKD2-4 (269.9 ng/ml), and PCKD5D (652.4 ng/ml). Multivariate regression analysis was used to assess the relationship between hepcidin and indicators of anemia, iron status, inflammation, and renal function.

In PCKD2-4 ($R(2) = 0.57$), only ferritin correlated with hepcidin. In ACKD2-4 ($R(2) = 0.78$), ferritin and soluble transferrin receptor were associated with hepcidin, whereas GFR was inversely correlated. In PCKD5D ($R(2) = 0.52$), percent iron saturation and ferritin were predictors of hepcidin.

Our study showed that there was statistically significant difference between the studied groups regarding FS, E/Ea' ratio with mean of FS 35.2 and 32.5 for group I and group II and 30.4 for control group while mean of E/Ea' ratio was 14 and 10 for group I and group II and 8 for control group that mean diastolic dysfunction (p value 0.002). There was no statistically significant difference between conservative group and dialysis group.

Chinali et al, [21] who studied Advanced Parameters of Cardiac Mechanics in Children with CKD and used ejection fraction instead of FS to assess systolic function showed no differences among groups in LV ejection fraction, with all patients with CKD showing normal values of ejection fraction (i.e., ejection fraction between 56%–75%).

Left ventricular hypertrophy (LVH) develops early in the course of CKD and is thought to maintain cardiac function and reduce left ventricular wall stress during conditions of increased afterload and preload [22].

In the present study we found that there was high statistically significant difference in LVMI among studied groups (p value <0.001) as LVMI is increased in group I and group II CKD patients with mean 123.1 and 97.2gm/m²

than control group where mean was 11.4 gm/m^2

Mitsnefes et al. [23] who studied Left Ventricular Mass and Systolic Performance on Twenty-five children with CRI, 12 undergoing chronic dialysis, and 24 controls and used LVMI to height found that Both children with CRI ($29.3 \pm 6.7 \text{ g/m}^{2.7}$) and children undergoing dialysis ($44.9 \pm 15.9 \text{ g/m}^{2.7}$) had elevated LVM index compared with the control group ($22.2 \pm 6.1 \text{ g/m}^{2.7}$, $P < 0.001$) and Children undergoing chronic dialysis had significantly higher LVM index compared with patients with CRI ($P < 0.001$).

We studied the correlation between anemia and cardiac dysfunction and found that there was statistically significant correlation between anemia and cardiac dysfunction among the studied groups as cardiac dysfunction is more prevalent in anemic than non-anemic group as 60.6 % of anemic patients has cardiac dysfunction.

Ehsan et al . [4] who studied Prevalence of Cardiac Abnormalities in Children with Chronic Kidney Disease found that among the risk factors of cardiac abnormalities, anemia and was associated with raised LVMI and LVH and was also statistically significant ($P = 0.05, 0.01$). The total prevalence of cardiac abnormality was found in 66.9% patients. The echocardiographic findings showed that among all CKD grades, the total number of patients with raised LVMI were 68 (64%). Diastolic dysfunction was found in 13 (12.2%) patients while systolic dysfunction in 12 (11.3%) patients.

On studying ECHO parameters, there was statistically significant correlation between serum hepcidin and FS, E/Ea' ratio and LVMI.

Hyang et al. [24] who studied Relationship between Cardiac Geometry and Serum Hepcidin in Chronic Kidney Disease found that although EF and E/e' were not significantly associated with high serum hepcidin, RWT and LVMI were significantly associated with high serum hepcidin levels in univariate logistic regression analysis.

On the contrary, Yao-Peng Hsieh et al. [25] who studied Hepcidin relation with left ventricular mass index in chronic kidney disease patients. The study was done between March 2009 and April 2010 in the Nephrology Department of Changhua Christian Hospital and included 146 CKD patients (84 males, 62 females) in stages 1-5 who did not require dialysis. The result of the study was there were negative correlations between the serum hepcidin level and the LVM and LVMI ($P = 0.04$ and $P = 0.005$, respectively).

CONCLUSION

Serum hepcidin levels are a good biomarker for iron status and cardiac dysfunction in patients with CKD. Early and regular echocardiographic studies of all children with CKD on hemodialysis, as they are prone to the development of cardiac dysfunctions in the early state of the disease. Evaluation and treatment of anemia in children with CKD, as it is an important factor of cardiac dysfunction in children with CKD. In future, anti hepcidin and gene therapy may play a role in the treatment of anemia.

ABBREVIATIONS

Ca	Calcium	HB	Haemoglobin
CKD	Chronic kidney disease	IDA	Iron-deficiency anemia
CRF	Chronic renal failure	IHD	Ischemic heart disease
CRI	Chronic renal impairment	IVSTD	Interventricular septal thickness in diastole
CVD	Cardiovascular disease	K	Potassium
HD	Hemodialysis	LVH	Left ventricular hypertrophy
E/EA'	Trans mitral to mitral annular early diastolic velocity ratio	LVIDD	Left ventricular internal diameter in diastole
EF	Ejection fraction	LVMI	Left ventricular mass index
ELISA	Enzyme-linked immunosorbent assay	Na	Sodium
EPO	Erythropoietin	Ph	Phosphorus
ESA	Erythropoietin stimulating agents	PTH	Parathyroid hormone
ESRD	End-stage renal disease	PWTD	Posterior wall thickness in diastole
FS	Fractional shortening	RWT	Relative wall thickness
GFR	Glomerular filtration rate	TIBC	Total iron binding capacity

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AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.

All authors have contributed to authorship, have read and approved the manuscript.

Conception and design of study: all authors

Acquisition of data: all authors.

Analysis and/or interpretation of data: all authors

Drafting the manuscript: all authors

Revising the manuscript critically for important intellectual content: all authors

Approval of the version of the manuscript to be published: All authors.

STATEMENTS

Consent for publication

The attached manuscript its contents and materials have not been previously reported at any length or being considered for publishing elsewhere.

Ethics approval and consent to participate

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Faculty of Medicine, Benha University Hospital and informed written consent was obtained in every case from their legal guardians.

Availability of data

The authors have indicated that the data and material are factual and genuine.

Conflict of interest

The authors have indicated they have no potential conflicts of interest to disclose.

Funding

The authors have indicated they have no financial relationships relevant to this article to disclose.

Acknowledgments

Authors would like to thank all patients and their family members for their valuable contributions to the study.

Submitted: 08/01/2022

Accepted: 03/04/2022

Published Online: 30/06/2022