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THE ROLE OF HEPCIDIN AND SOLUBLE TRANSFERRIN RECEPTOR LEVEL FOR THE EVALUATION OF ANEMIA IN ADVANCED RENAL FAILURE

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ABSTRACT

Background: Anemia is a frequent complication of chronic kidney disease (CKD), particularly in advanced stages, contributing to increased morbidity and mortality. The objective is to study the relation between iron state and hepcidin as a marker for iron metabolism and soluble transferrin receptor as a marker for erythropoiesis. **Method:** This prospective case series included 60 patients with end-stage renal failure on regular dialysis at Ibn Sina Teaching Hospital, Mosul, between June and September 2022. The study aimed to evaluate the relationship between iron status, hepcidin as a marker of iron metabolism, and soluble transferrin receptor (sTfR) as a marker of erythropoiesis. Thirty age- and sex-matched healthy controls were included for comparison of serum hepcidin levels. Laboratory investigations comprised complete blood count, reticulocyte percentage, erythrocyte sedimentation rate, serum iron, total iron-binding capacity (TIBC), transferrin saturation, ferritin, hepcidin, sTfR, renal function, liver profile, and electrolytes. **Results:** 60 patients (26 males, 34 females, aged 20–70 years), diabetes mellitus was the leading cause of CKD. Results demonstrated reduced hemoglobin, serum iron, TIBC, transferrin saturation, and sTfR, while ferritin was elevated. Hepcidin showed no significant association with the underlying etiology, but correlated positively with serum iron, transferrin saturation, and ferritin, and negatively with estimated glomerular filtration rate. It also showed a significant positive correlation with creatinine and urea (p=0.024). Soluble transferrin receptor correlated positively, though not significantly, with hemoglobin, serum iron, ferritin, transferrin saturation, red cell count, and corrected reticulocyte percentage. **Conclusion:** anemia in CKD is multifactorial with complex dysregulation of iron metabolism. Hepcidin regulation appears to be influenced by multiple factors, limiting its reliability, while sTfR provided a poor reflection of erythropoiesis in this patient group.

KEYWORDS: Hepcidin, Soluble, Transferrin, Receptor, Anemia, Renal, Failure.

INTRODUCTION

Chronic kidney disease (CKD) is a prevalent, largely preventable cause of morbidity and mortality worldwide, imposing substantial economic and healthcare burdens—particularly in advanced stages requiring dialysis or transplantation.[1] CKD is defined by persistent kidney damage and/or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² for ≥3 months, irrespective of etiology.[2] Its prevalence rises steeply with age and is higher in men; diabetes and hypertension are major contributors.[3] The incidence of end-stage renal disease (ESRD) is greatest in highly developed regions, with over one million patients on dialysis globally[4] Disease staging has evolved from the KDOQI framework—which stratifies CKD by GFR into five stages (G1–G5)—to the KDIGO schema that integrates GFR, albuminuria (A1–A3), and cause, commonly visualized in a two-dimensional "heat map" prognostic model.[5] Anemia is an early and progressive complication of CKD, associated with cardiovascular events, cognitive impairment, reduced quality of life, and higher hospitalization and mortality.[6] Its prevalence increases with declining GFR and is particularly pronounced in diabetes and stage 5 CKD.[7] Pathogenesis is multifactorial: impaired erythropoiesis from inadequate renal erythropoietin (EPO) production; absolute or functional iron deficiency; shortened red cell lifespan; and contributory factors such as inflammation, secondary

hyperparathyroidism, nutritional deficiencies, uremic toxins, and dialysis-related blood loss.[8] Iron metabolism in CKD is complex. Systemic iron trafficking relies on dietary absorption and macrophage-mediated recycling, with hepcidin—a hepatocyte-derived peptide—serving as the master regulator via ferroportin degradation, thereby restricting intestinal iron absorption and macrophage iron export.[9] In CKD, hepcidin is frequently elevated due to inflammation (notably IL-6–driven), reduced renal clearance, and suppressed erythropoiesis, leading to iron sequestration and reduced iron availability for erythropoiesis.[10] Assessment of iron status traditionally employs serum iron, total iron-binding capacity (TIBC), transferrin saturation (TSAT), and ferritin; however, ferritin's role as an acute-phase reactant can obscure iron deficiency in inflammatory states.[11] Soluble transferrin receptor (sTfR)—the cleaved ectodomain of cellular TfR1—reflects cellular iron demand and erythropoietic activity, helping distinguish iron-deficiency anemia (IDA) from anemia of chronic disease (ACD) and identify mixed IDA+ACD, with minimal confounding by inflammation.[12] Additional indices (percentage of hypochromic red cells, reticulocyte hemoglobin content) offer real-time insights into functional iron availability for erythropoiesis.[13] Evaluation of anemia in CKD requires exclusion of alternative causes and incorporates history, examination, complete blood count with reticulocytes, iron studies, B12/folate, and inflammatory biomarkers (CRP, ESR); these inform diagnosis and guide therapy, including iron supplementation and erythropoiesis-stimulating agents.[14] Ancillary tests (zinc protoporphyrin, EPO titers) can refine assessment in select scenarios.[15] Aim of study to reveal the relation between iron state and hepcidin as a marker for iron metabolism and to show the relation between iron state and soluble transferrin receptor as a marker for erythropoiesis.

METHOD

This prospective case series enrolled 60 adults (≥18 years) with clinically confirmed chronic kidney disease (CKD) on regular hemodialysis, admitted to Ibn Sina Teaching Hospital, Mosul, between June and September 2022. All patients were receiving standard anemia management (Eprex®/epoetin alfa, folic acid, and iron when indicated). Exclusion criteria were age <18 years and pregnancy. Ethical approval was granted by the Ministry of Health / Nineveh Health Department (No. 3541; April 3, 2022), and written informed consent was obtained from all participants. In addition, serum hepcidin was measured in 30 age- and sex-matched healthy volunteers used as controls. A structured questionnaire captured demographics, CKD history (time since diagnosis, dialysis start date, etiology), anemia symptoms (e.g., pallor, dyspnea, palpitations), comorbidities, medications, and family history. General and systemic examinations were performed. Seven milliliters of peripheral venous blood were drawn pre-dialysis using standard venipuncture. EDTA-anticoagulated blood was gently inverted and analyzed within 1 hour for complete blood count (CBC), reticulocyte percentage, and erythrocyte sedimentation rate (ESR). Remaining blood was placed in serum separator tubes, allowed to clot at room temperature for 30 minutes, and centrifuged at 2000 rpm for 20 minutes. Serum aliquots (100 µL) were reserved for biochemical assays and ELISA determinations. Hematologic indices were measured on a Phoenix NCC-3300 autoanalyzer (Neomedica, Serbia). ESR was determined by the Westergren method. Reticulocytes were stained with 40% Brilliant Cresyl Blue. Biochemistry included serum iron, total iron-binding capacity (TIBC), blood urea, creatinine, total protein, albumin, and liver function tests on a Cobas c111 analyzer (Roche, Germany), and electrolytes on an ABL9 analyzer. Transferrin saturation (TSAT) was calculated as (serum iron/TIBC)×100. Serum ferritin was quantified using the Demeditec Ferritin ELISA (DE4408; Germany). Serum hepcidin and soluble transferrin receptor (sTfR) were measured using CUSABIO ELISA kits (CSB-E13062h and CSB-E09100h, respectively), following manufacturers' protocols. Statistical analyses were conducted in SPSS (IBM). Descriptive statistics summarized continuous (mean±SD or median [IQR]) and categorical data (n, %). Group comparisons for categorical variables used Chi-square tests; continuous variables were compared with one-way ANOVA, as appropriate. A two-sided $p \leq 0.05$ was considered statistically significant.

RESULTS

 Patient demographics: 60 cases, aged 20–70 years; 43.3% male and 56.7% female.

 Etiology: Diabetes mellitus (51.7%) was the most common, followed by hypertension (31.7%), organic kidney disease (10%), and autoimmune causes (6.7%) as in fig. 1 and 2 and table 1.

 Hematological findings

- Majority (80%) had moderate anemia, 8% severe, and 12% mild.
- Low RBC in 83.3% of patients.
- Corrected reticulocyte count was normal in 88%.
- Mean Hb = 8.74 g/dl; Hct = 27.03%.
- WBC and platelet counts largely normal as in table 2.

 Iron indices

- Serum iron low in 75%.
- TIBC low in 93.3%.
- Transferrin saturation normal in 71.6%.
- Ferritin elevated in 81.6%.
- Mean serum hepcidin = 39.48 ng/ml (higher than controls, p=0.048).
- sTfR low in most patients (only 8.3% normal) as in table 3.

 Biochemical findings

- Creatinine (mean 9.12 mg/dl), Urea (mean 128.82 mg/dl) markedly elevated.

- Albumin (mean 3.72 g/dl) slightly low.
- Phosphate high (mean 5.10 mg/dl).
- Electrolyte imbalance noted as in table 4.

Correlations

- Hepcidin correlated negatively with Hb (NS, p=0.198) and GFR (NS, p=0.886).
- Positive correlation with serum iron (p=0.043), transferrin saturation (p=0.018), ferritin (p=0.037), and urea (p=0.024).
- Positive but non-significant correlation with creatinine.
- sTfR showed only non-significant positive correlations with Hb, serum iron, transferrin saturation, ferritin, RBC count, and corrected reticulocytes as in fig 3 and 4.

Figure 1: Age distribution of patients with advanced renal failure

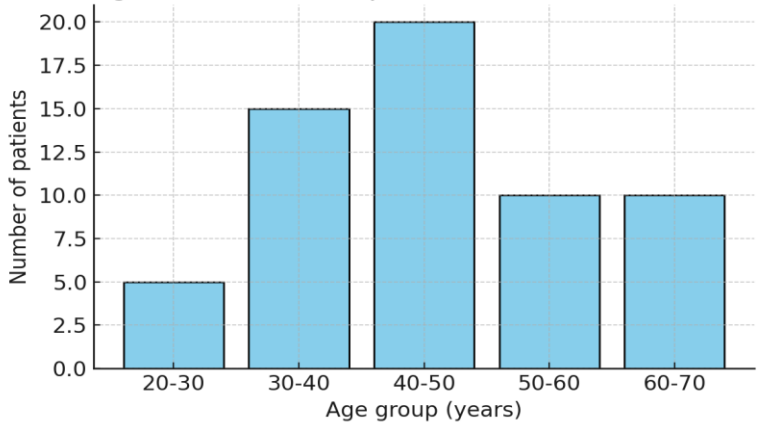

Figure 2: Gender distribution of patients

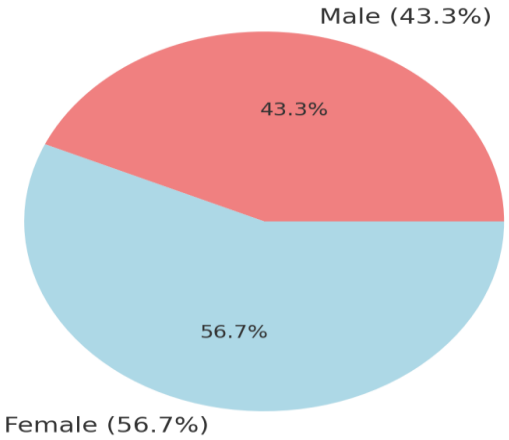

Table 1: Etiological parameters.

Etiology	Male (n=26)	Female (n=34)	Total (%)
Hypertension	11 (42.3%)	8 (23.5%)	19 (31.7%)
Diabetes Mellitus	10 (38.5%)	21 (61.8%)	31 (51.7%)
Systemic autoimmune	0 (0.0%)	4 (11.8%)	4 (6.7%)
Organic kidney related	5 (19.2%)	1 (2.9%)	6 (10.0%)

Table 2: Hematological parameters.

Parameter	Mean	Min	Max
Hb (g/dl)	8.74	4.9	10.6
Hct (%)	27.03	15.0	32.6
MCV (fl)	87.89	64.0	101.4
MCH (pg)	28.58	21.8	33.0
RBC (x10^12/l)	3.27	1.89	5.8
Retic %	2.43	0.8	15.0

Corrected Retic	1.4	0.32	3.47
WBC (x10^9/l)	6.44	1.89	15.9
Platelets (x10^9/l)	188.6	77.0	433.0
ESR (mm/hr)	15.55	2.0	73.0

Table 3: Iron indices

Parameter	Mean	Min	Max
Serum iron (µmol/l)	8.07	2.8	15.0
TIBC (µmol/l)	38.21	22.9	108.6
Transferrin saturation (%)	21.87	0.22	52.0
Ferritin (µg/l)	569.55	115.0	2000.0
Hepcidin (ng/ml)	39.48	10.9	201.2
sTfR (mg/l)	1.29	0.19	2.3

Table 4: Biochemical parameters.

Parameter	Mean	Min	Max
Creatinine (mg/dl)	9.12	4.5	18.8
Urea (mg/dl)	128.82	54.0	190.0
Albumin (g/dl)	3.72	2.0	4.9
Total Protein (g/dl)	6.98	2.4	10.0
SGOT (u/l)	20.04	3.6	127.0
SGPT (u/l)	12.46	4.0	48.0
ALP (u/l)	130.0	13.0	550.0
TSB (mg/dl)	0.39	0.1	1.6
PO4 (mg/dl)	5.1	1.9	9.1
Na (mmol/l)	135.45	113.0	143.0
K (mmol/l)	5.51	3.1	8.1
Calcium (mg/dl)	8.5	2.2	11.0

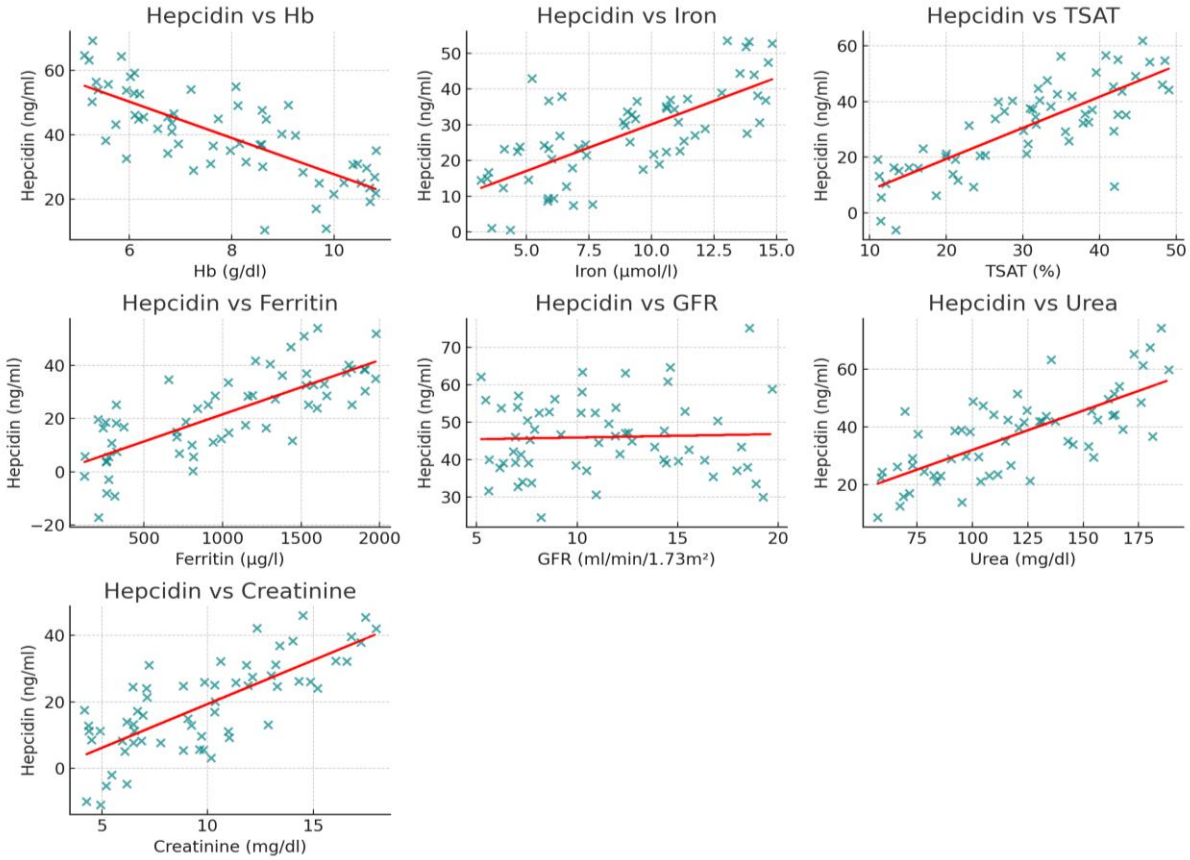

Fig 3: Hepcidin correlations.

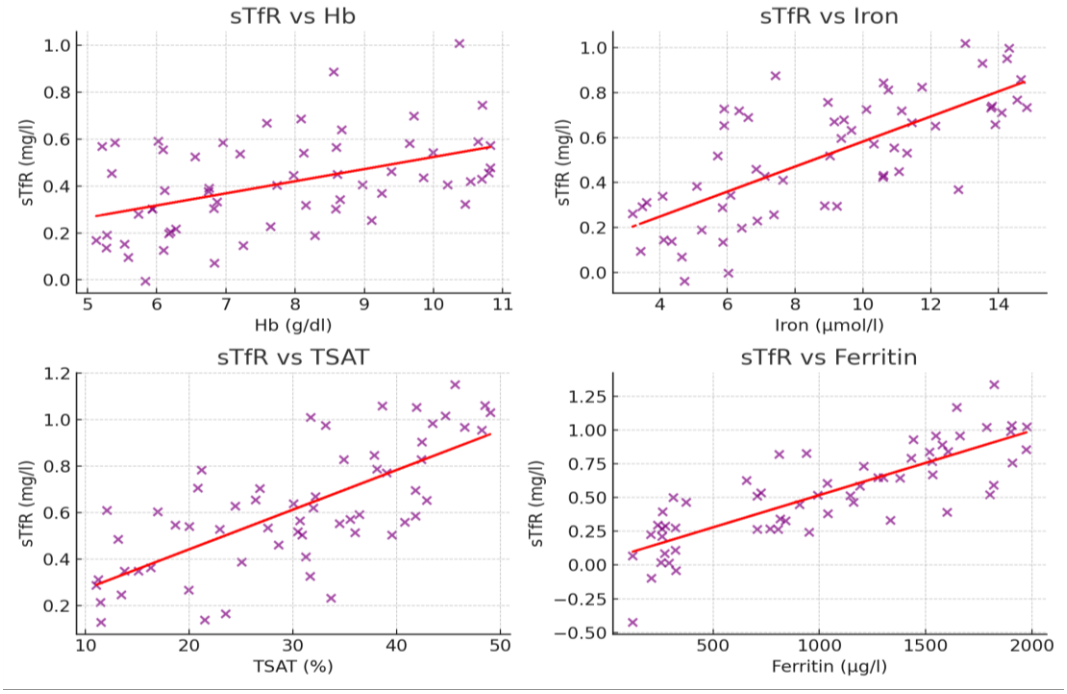

Fig 4: sTfR correlations.

DISCUSSION

Anemia in chronic kidney disease (CKD) is a multifactorial disorder arising from inadequate erythropoietin (EPO) production, disturbed iron metabolism, and chronic inflammation, which complicates defining a discrete cause.[6] In this prospective study of 60 hemodialysis patients, hematological indices and iron biomarkers were analyzed, with special attention to hepcidin and soluble transferrin receptor (sTfR). The cohort included 43.3% males and 56.7% females, with diabetes mellitus as the leading etiology of CKD, similar to reports from Singh et al.[16] and Uddin et al.[17] Hemoglobin, hematocrit, and RBC counts were below normal, confirming previous findings by Al-Rubaie et al.[18] Habib et al.[19] and Singh et al.[16] Despite EPO therapy, anemia persisted, consistent with functional iron deficiency induced by erythropoiesis-stimulating agents.[20] The anemia pattern was normocytic normochromic, agreeing with Saadi et al.[21] Mean serum iron, TIBC, and TSAT were low, similar to Al-Rubaie et al.[21] and Xu et al.[22] Although ferritin was elevated, consistent with Saadi et al.[21] Al-Rubaie et al.[18] and ul Haque.[23] this reflects functional iron deficiency where iron is sequestered despite adequate stores.[24] Serum hepcidin averaged 39.48 ng/mL, lower than values in Al-Rubaie.[18] and Kamal.[25] It correlated positively with serum iron, ferritin, and TSAT, as observed in Xu et al.[22] Ibrahim et al.[26] The significant inverse correlation with eGFR mirrored results of Petres et al.[27] Zaritsky et al.[28] Hepcidin also correlated positively with urea and creatinine, supporting Malyszko et al.[29] These findings highlight the multifactorial regulation of hepcidin, influenced by renal clearance and inflammation Mean sTfR (1.29 mg/L) was comparable to Der-Cherng et al.[30] but lower than in Majeed et al.[32] No significant correlation with hemoglobin or iron indices was found, aligning with Lorenzo et al.[33] though Yin et al.[34] reported inverse correlations. Discrepancies may relate to ESA dosing, treatment compliance, or timing of sampling relative to dialysis.[35]

CONCLUSION

Multiple factors affect hepcidin level in advanced renal failure, so the study of hepcidin level is inconclusive. Soluble transferrin receptor study level is valuable in assessing erythropoiesis in advanced renal failure. Most of our patients may have resistance to erythropoiesis stimulating agents and might, in part, be attributed to inadequate dialysis or in sufficient iron supply. Large percentage of patients are not compliant to their medications.

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