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Evaluation of transferrin saturation and serum ferritin in assessing body iron status in patients with end stage renal disease

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Abstract
Background: Renal failure causes anemia for many. Serum iron and transferrin saturation indicate hemoglobin synthesis iron availability. Total body iron is measured by serum ferritin. For optimal recombinant human erythropoietin benefit, adequate iron reserves are needed. Recombinant erythropoietin success depends on iron status assessment. The study aims to evaluate the effectiveness of traditional indicators (serum iron, total iron binding capacity, transferring saturation, and serum ferritin) in monitoring body iron status and determining the impact of recombinant human erythropoietin therapy on end-stage renal disease patients.
Methods: From June 1 to November 10, 2010, 40 end-stage renal disease patients on regular hemodialysis from Medical City's Renal Transplant Centre and Dialysis Unit participated in this study. We obtained clinical data. Manually measured blood iron, total iron binding capacity, transferrin saturation, ferritin, albumin, creatinine, and C-reactive protein. 30 healthy people were in the control group.
Results: End stage renal disease (ESRD) patients had a mean age of 45.1 years, with 60% being male. They exhibited significantly lower PCV (25.3%) and higher platelet and WBC counts compared to healthy controls. High serum ferritin was seen in 72.5% of patients, while 37.5% had functional iron deficiency. ESRD was associated with lower serum albumin and higher serum creatinine levels, with significant correlations between PCV, serum albumin, and serum creatinine.
Conclusion: About 72.5% of end stage renal disease (ESRD) patients had high serum ferritin (≥300 ng/ml), which was not a reliable index for iron stores and indicated an acute phase response. Combining transferrin saturation and serum ferritin showed low sensitivity in diagnosing iron status, determining iron status in only 47.5% of ESRD patients. The coexistence of anemia of chronic disorder and iron deficiency obscures the effectiveness of classical indices in assessing body iron status.

Keywords: Transferrin, saturation, serum ferritin, body iron, end stage, renal disease

Introduction
Chronic kidney disease (CKD) is a prevalent global health issue, with anemia being a common complication that significantly increases the risk for cardiovascular disease, accelerates renal failure progression, and reduces quality of life [1]. Studies such as the one by Obrador *et al*. revealed that 68% of predialysis patients with advanced CKD requiring renal replacement therapy had a hematocrit below 30%, with 51% having a hematocrit under 28% [2]. While anemia is rare in early CKD stages, prevalence rises sharply to 5.2% in stage III and 44.1% in stage IV [3]. Anemia in chronic renal failure (CRF) primarily results from inadequate erythropoietin synthesis, with serum erythropoietin levels insufficient for the degree of anemia [4]. Additional causes include blood loss from vascular access puncture sites and gastrointestinal bleeding. Iron deficiency frequently coexists in these patients, and its management is crucial as it can enhance anemia correction and reduce the need for erythropoiesis-stimulating agents (ESAs). Partial correction of anemia, while not complete, is associated with better outcomes in CKD patients. The introduction of ESAs and intravenous iron preparations has significantly improved anemia management in CKD, enabling maintenance of hemoglobin (Hb) levels within targeted ranges and effective iron deficiency treatment [1]. Recombinant human erythropoietin (r-HuEPO) therapy has substantially enhanced the quality of life and outcomes for hemodialysis (HD) patients [1]. However, resistance to r-HuEPO, often due to iron deficiency, remains a significant

challenge. Nephrologists must carefully manage resources and optimize treatment strategies [1]. Most CRF patients achieve target Hb levels with low doses (50-150 IU/kg/week) of r-HuEPO and 1500-3000 mg/year of parenteral iron. However, about 25% of dialysis patients exhibit poor response and require higher doses (>200 IU/kg/week). This resistance is commonly linked to comorbid conditions, particularly inflammatory states, which can cause acute or chronic resistance to r-HuEPO [4]. Conventional iron status tests, such as serum iron, total iron-binding capacity (TIBC), transferrin saturation (TSAT), and ferritin, are widely used but are significantly affected by acute phase responses, complicating clinical interpretation [5]. This underscores the need for noninvasive, sensitive iron deficiency detection methods, prompting the development of newer, less-variable biomarkers [6]. Current laboratory biomarkers, whether newer or classical, lack ideal predictive ability when used alone to diagnose iron deficiency as per the iron challenge test. There is insufficient evidence on the diagnostic performance of combinations of newer biomarkers or the integration of newer and classical markers for iron deficiency diagnosis [6]. The influence of various factors on the effectiveness and clinical utility of these newer iron status markers remains largely unexplored [6]. Aim of Study: To evaluate the efficacy of classical indices (serum iron, TIBC, TSAT, and serum ferritin) in assessing body iron status in ESRD patients, which impacts iron and r-HuEPO treatment strategies. This evaluation seeks to clarify the clinical utility of these biomarkers in managing iron status and optimizing anemia treatment in ESRD.

MethodS

From June 1, 2010, to November 10, 2010, 40 patients with end-stage renal disease (ESRD) (24 males, 16 females) aged 21-69 years were studied. All patients were on chronic hemodialysis (HD) for 4 to 60 months. Each HD session began with a 5000 IU bolus dose of unfractionated heparin and concluded with a 4000 IU subcutaneous dose of recombinant human erythropoietin (r-HuEPO). Twenty-seven patients received regular parenteral iron therapy for at least three months prior to the study, while the rest had irregular or no iron supplementation. Dialysis was conducted using a polysulfone membrane.

Exclusion criteria

Patients with active infection or inflammation, active bleeding, malignancy, recent blood transfusions (within three months), or rejected transplanted kidneys were excluded. Clinical data were collected via questionnaire, including the duration and causes of chronic renal failure (CRF), medical and drug history, and details on EPO and iron therapy, HD frequency and duration, and bleeding history.

Controls

Thirty healthy controls, matched for age and sex with the patient group, were included. They had no history of chronic illness or renal disease.

Blood Sampling and Processing: Venous blood (10 ml) was drawn using a disposable syringe from each patient and control.

1. **EDTA Tube:** 2 ml was mixed and used within 2 hours for packed cell volume (PCV), total white blood cell (WBC) count, and platelet count.
2. **Plain Tube:** 6 ml was left to clot, incubated at 37°C for 1 hour, and centrifuged. The serum was collected for serum iron, total iron-binding capacity (TIBC), ferritin, creatinine, and albumin measurements.
3. **Plain Tube for CRP:** 2 ml was centrifuged for C-reactive protein (CRP) assay.

Hematological Tests

PCV was measured using microhematocrit methods; WBC count was determined via manual dilution and counting in a Neubauer chamber; platelet count was similarly performed using ammonium oxalate dilution and Neubauer chamber counting [7].

Biochemical Tests

Serum iron was measured using a Randox spectrophotometric kit, based on iron's reaction with a chromogen to form a blue chromophore [8]. TIBC was measured similarly, reflecting transferrin's iron-binding capacity [9]. Transferrin saturation (TSAT) was calculated as serum iron/TIBC × 100 [10]. Serum ferritin was measured using ELISA, providing a colorimetric response proportional to ferritin concentration [11]. Serum creatinine and albumin were measured by Randox kits using colorimetric methods [12].

CRP Measurement

CRP was assessed using a latex agglutination assay, with positive results indicating CRP levels ≥ 6 mg/l [13].

Statistical Analysis

Statistical analysis was performed using SPSS (version 20) and Excel 2007. Data were expressed as mean ± SD for numerical variables and number and percent for categorical variables. Differences between groups were assessed using Student’s t-test or ANOVA, and associations were tested with the Chi-square test. A p-value < 0.05 was considered statistically significant.

Results

End-stage renal disease (ESRD) had a strong effect on most hematological and biochemical parameters compared to healthy controls, except for total iron binding capacity (Cohen’s $d = 0.45$). The most affected parameters were packed cell volume (PCV) and serum ferritin (Cohen’s $d = 4.51$ and 3.17, respectively). Mean PCV was significantly lower in patients (25.3%) compared to controls (41.1%). ESRD patients had significantly higher platelet and WBC counts, lower mean TSAT and serum iron, but a higher serum ferritin. Serum albumin was significantly lower, while serum creatinine was significantly higher in ESRD patients compared to controls. As in Table 1.

Table 1: The case-control difference in mean of hematological and biochemical parameters

	Healthy controls	Patients with ESRD	P (t-test)	Difference in mean	Cohen's d
PCV			<0.001	-15.8	-4.51
Range	(36-45)	(12-39)			
Mean	41.1	25.3			
SD	2.6	6.5			
SE	0.47	1.03			
Platelets count (× 10^9/L)			<0.001	111.5	1.49
Range	(150-233)	(110-610)			
Mean	174.2	285.7			
SD	23.2	148.1			
SE	4.23	23.42			
3. WBC count (× 10^9/L)			<0.001	4	2.48
Range	(4-7.5)	(3.8-15.5)			
Mean	5.4	9.4			
SD	0.9	3.1			
SE	0.16	0.49			
Serum Iron conc (µg/dl)			<0.001	-41.5	-1.81
Range	(50-155)	(16-120)			
Mean	104.5	63			
SD	35.1	29.6			
SE	6.41	4.69			
Total Iron Binding capacity (µg/dl)			0.21[NS]	-21.1	-0.45
Range	(260-387)	(132-471)			
Mean	320.3	299.2			
SD	42.2	84.4			
SE	7.7	13.35			
TSAT (%) Range	(16-51.7)	(7.6-55)	<0.001	-10.6	-1.23
Mean	33.3	22.7			
SD	12.1	12.2			
SE	2.22	1.93			
Serum Ferritin conc					
(ng/ml)			<0.001	373.8	3.17
Range	(12.5-210)	(50-830)			
Mean	66.6	440.4			
SD	56.9	228.5			
SE	10.39	36.13			
Serum Albumin conc					
(g/dl)			<0.001	-1.2	-3.3
Range	(3.8-4.4)	(1.7-4.1)			
Mean	4	2.8			
SD	0.2	0.7			
SE	0.04	0.11			
Serum Creatinine conc					
(mg/dl)			<0.001	5	4.16
Range	(0.5-1)	(1.5-12.5)			
Mean	0.7	5.7			
SD	0.1	2.4			
SE	0.02	0.38			

Table 2: Frequency distribution of ESRD patients by abnormal iron indices

	N	%
1. High Serum Ferritin (300+ ng/ml)		
Negative	11	27.5
Positive	29	72.5
Total	40	100.0
2. Low Serum Iron conc (<50 µg/dl)		
Negative	24	60.0
Positive	16	40.0
Total	40	100.0
3. Total Iron Binding capacity-categories		
Low (<259 µg/dl)	14	35.0
Normal range (259-388 µg/dl)	21	52.5
High (>388 µg/dl)	5	12.5
Total	40	100.0
4. Low TSAT (<20%)		
Negative	23	57.5
Positive	17	42.5
Total	40	100.0

The frequency of high serum ferritin (>300) was observed in 72.5%. A low TSAT (<20%) was observed in 42.5% of ESRD patients on HD. The frequency of low serum iron (less than 50 µg/dl) was 40%. An abnormally low total iron binding capacity (<259 µg/dl) was observed in 35% of ESRD, while an abnormally high binding capacity (>388 µg/dl) had a frequency of 12.5%, as shown in table 2.

Using TSAT and serum ferritin, iron status could be determined in 19 (47.5%) patients only; 15 (37.5%) had adequate (or normal) iron status, 2 (5%) had absolute iron deficiency, 2 (5%) had iron overload. In the remaining 21 (52.5) patients, iron status was undetermined; 7 (17.5%) patients had high serum ferritin with low TSAT (functional iron deficiency) as shown in table 3.

Table 3: Iron status in ESRD

Iron status	N	%
Diagnosed status	19	47.5
Adequate status (both Serum ferritin between 100-500 and TSAT between 20-50%)	15	37.5
Absolute iron deficiency (both Serum ferritin < 100 and TSAT<20)	2	5
Iron overload (both Serum ferritin > 500 and TSAT> 50)	2	5
Undetermined status	21	52.5
Serum ferritin >500 and TSAT < 20 (Functional iron deficiency)	7	17.5
Ferritin 100-500 and TSAT < 20	8	20
Ferritin > 500 and TSAT 20-50	6	15
Patients with high serum ferritin (>500)	15	37.5
True iron overload	2	5
Undetermined	13	32.5

Table 4 shows that high serum ferritin (>300) was linked with a lower percentage of poor TSAT (34.5%) than low ferritin (63.6%). The negative correlation between high serum ferritin and low TSAT was not statistically significant. High serum ferritin levels were related with a lower percentage of low serum iron (34.5%) than lower levels (54.5%). The negative correlation between high serum ferritin and low serum iron was not statistically significant. Higher serum ferritin levels were related with a lower percentage of ESRD patients with high TIBC (6.9%) than lower levels (27.3%). The negative correlation between high serum ferritin and high TIBC was not statistically significant.

Table 4: The rate of low TSAT, low serum iron, low and high TIBC by level of serum ferritin among patients group.

	Serum ferritin (300+ng/ml)				P-value
	Positive		Negative		
	N	%	N	%	
Low TSAT (<20%)					0.1[NS]
Not low	19	65.5	4		36.4
Low	10	34.5	7		63.6
Total	29	100.0	11		100.0
Low Serum Iron conc (<50 µg/dl)					0.25[NS]
Not low	19	65.5	5		45.5
Low	10	34.5	6		54.5
Total	29	100.0	11		100.0
Total iron binding capacity					0.22[NS]
Low TIBC(<259 µg/dl)	10	34.5	4		36.4
Normal TIBC (259-388 µg/dl)	17	58.6	4		36.4
High TIBC (>388 µg/dl)	2	6.9	3		27.3
Total	29	100.0	11		100.0

As shown in table 5, high serum ferritin (>300), low TSAT and low serum iron had no obvious or statistically significant effect on mean PCV. Avery low and very high TIBC were associated with a significantly lower mean PCV (22.1 and 21.8% respectively) compared to that in patients with normal TIBC (28.3%). CRP level had no obvious association with PCV, table 5. Serum albumin and creatinine levels had important linear association with PCV,

Table 5: The mean PCV by selected explanatory variables among patients with ESRD. PCV

	Range	Mean	SD	SE	N	P
High Serum Ferritin (300+ µg/ml) Negative	(18-35)	26.2	5.6	1.69	11	0.61[NS]
Positive	(12-39)	25.0	6.9	1.28	29	
Low TSAT (<20%) Negative	(13-39)	25.2	7.4	1.55	23	0.87[NS]
Positive	(12-33)	25.5	5.2	1.27	17	
Low Serum Iron conc (<50 µg/dl) Negative	(14-39)	26.1	6.7	1.37	24	0.37[NS]
Positive	(12-33)	24.2	6.2	1.56	16	
Total Iron Binding capacity-categories Low (<259 µg/dl)	(12-33)	22.1	6.7	1.80	14	0.006
Normal range (259-388 µg/dl)	(19-39)	28.3	5.5	1.20	21	
High (>388 µg/dl)	(18-27)	21.8	3.9	1.74	5	
Serum CRP Negative	(14-33)	23.5	5.8	1.51	15	0.07[NS]
6	(19-39)	28.9	6.0	1.73	12	
12+	(12-35)	24.1	6.8	1.89	13	

CRP was classified into negative CRP, low positive CRP (< 6 mg/l) and those with high serum CRP (> 12 mg/l). A stratified analysis for CRP level was done to adjust for the confounding effect of high serum CRP as an indication of inflammation on the association between serum ferritin (which is also a positive acute phase reactant in addition to reflecting body iron stores) and its effect on PCV. As shown in table 6, there was no significant association of high serum ferritin (≥300 ng/ml) with PCV at any level of CRP.

Table 6: The mean PCV by having a high serum ferritin level stratified by serum CRP level among patients with ESRD High Serum Ferritin (300+ ng/ml)

	Negative	Positive	P
Negative CRP Mean PCV	23.3	23.6	0.95[NS]
SE	4.84	1.60	
N	3	12	
Lowest Positive serum CRP (6) Mean PCV	27.3	29.8	0.52[NS]
SE	1.18	2.54	
N	4	8	
High serum CRP (12+) Mean PCV	27.3	22.7	0.28[NS]
SE	3.22	2.29	
N	4	9	

Discussion

The findings of this study highlight the significant impact of end-stage renal disease (ESRD) on various hematological and biochemical parameters, emphasizing the complexities in managing these patients. Diabetes mellitus and hypertension are well-recognized as the leading causes of chronic renal failure (CRF), together accounting for approximately 70% of cases [14]. In this study, the cause of CRF was unknown in 35% of patients, with hypertension constituting 25%, followed by diabetes mellitus (12.5%) and glomerulonephritis (12.5%). This differs from Al-Mukhtar's study, where chronic glomerulonephritis (GN) was the most frequent cause (35.7%), with unknown causes in 28.5%, hypertension in 14%, and diabetic nephropathy in 9% of cases [15]. The mean age of ESRD patients in this study was 45.1 years, with a male-to-female ratio of 1.5:1, which is consistent with Al-Mukhtar's findings (mean age 42.9 years, male-to-female ratio 1.5:1) and Junger *et al*.'s observation of a higher incidence of ESRD in males across all age groups [16]. These demographic similarities between the study groups suggest that age and gender do not significantly influence the outcomes of ESRD treatment. Anemia is a prevalent complication of CKD, primarily due to deficient erythropoietin (EPO) production [17]. The mean packed cell volume (PCV) was significantly lower in ESRD patients (25.3%) compared to healthy controls (41.1%), as shown in Table 1 This finding underscores the severity of anemia in ESRD, corroborating Al-Mukhtar's report of 84.3% anemia prevalence among ESRD patients [15]. Platelet and WBC counts are significantly affected by ESRD. This study found a statistically significant increase in platelet count (mean difference of 111.5 × 10^9/L) and WBC count (mean difference of 4 × 10^9/L) in ESRD patients compared to healthy controls (Tables 4 and 5). Alghythan's study similarly reported increased platelet and WBC counts in CRF patients on hemodialysis (HD) [18]. EPO therapy at high doses can enhance platelet production and activity independently of its erythropoietic effects [19]. This is corroborated by findings from Streja *et al*., who observed increased relative iron depletion and thrombocytosis in long-term HD patients receiving high-dose r-HuEPO [20]. Iron metabolism in ESRD patients is profoundly disrupted. This study revealed significantly lower serum transferrin saturation (TSAT) and serum iron levels in ESRD patients compared to controls (mean differences of 10.6% and 41.5 µg/dl, respectively), Kalantar-Zadeh *et al*. noted that iron deficiency is common in CRF patients, exacerbated by factors such as frequent blood loss and impaired iron absorption [21]. Although the total iron-binding capacity (TIBC) was slightly lower in ESRD patients, this reduction was not statistically significant, likely due to concurrent iron deficiency which increases TIBC. Serum ferritin levels were significantly higher in ESRD patients (mean difference of 373.8 ng/ml), indicating an inflammatory state rather than iron stores. High serum ferritin is often associated with inflammation and EPO resistance, complicating the interpretation of iron status in CKD patients [22]. This study found that 37.5% of patients had TSAT < 20 with normal or low serum ferritin, suggesting functional iron deficiency [21]. CRP, a marker of inflammation, was elevated in 32.5% of ESRD patients. Although CRP levels did not significantly correlate with PCV, elevated CRP is linked to EPO resistance and inflammation, contributing to poor anemia management [23]. Biochemical parameters such as serum albumin and creatinine were also significantly affected. ESRD patients had significantly lower serum albumin (mean difference of 1.2 g/dl) and higher serum creatinine (mean difference of 5 mg/dl) compared to controls. Hypoalbuminemia in dialysis patients is associated with increased morbidity and mortality, influenced by factors such as malnutrition and inflammation [24,25]. This study found significant positive and negative correlations between PCV and serum albumin, and PCV and serum creatinine, respectively, aligning with findings from Leavey and Ifudu [26, 27].

Conclusion

Approximately 72.5% of ESRD patients had high serum ferritin (≥300 ng/ml), indicating it is not a reliable index for iron stores and often reflects an acute phase response. When combined with transferrin saturation, the sensitivity for diagnosing iron status in ESRD patients was low, accurately determining iron status in only 47.5% of cases. The presence of anemia of chronic disorder and iron deficiency complicates the interpretation of classical indices like serum iron, TIBC, TSAT, and serum ferritin, reducing their effectiveness in assessing body iron status.

Conflict of Interest

Not available

Financial Support: Not available.

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