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Soluble Transferrin Receptor Is a Promising Marker of Iron Deficiency Anemia in Prevalent Hemodialysis Patients

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ABSTRACT

Background: Serum soluble transferrin receptor (STfR) is a vital marker for iron status assessment in inflammatory conditions.

Objective: evaluation of serum STfR usefulness in iron deficiency anemia detection in prevalent hemodialysis patients.

Patients and Method: This case-control study included 80 end-stage renal disease (ESRD) patients on conventional hemodialysis (HD) divided into 40 patients with c-reactive protein (CRP)>10 mg/l, 40 patients with CRP<10 mg/l and 8 healthy controls. Serum STFR was measured for all patients and controls.

Results: STfR can predict iron deficiency anemia in hemodialysis patients at cut-off value of 12.5 mg/l with an area under curve 0.949. The STfR was positive in 85% in patients with CRP<10 mg/l and 92.5% in patients with CRP>10 mg/l (P-value 0.288). Patients who have elevated STfR have a risk of 1.22 times to have iron deficiency anemia if CRP <10 mg/l (odds ratio: 1.22) and 3.14 times if CRP>10 mg/l (odds ratio: 3.14). There was a significant difference between patients with CRP<10 mg/l, CRP>10 mg/l, and control in hemoglobin and STfR level with P-value 0.0001 and 0.0001 respectively. Post Hoc analysis showed significant difference between patients with CRP<10 mg/l and CRP>10 mg/l in STfR p-value 0.0001 despite no significant difference in hemoglobin (p-value 0.642) and classic iron markers (s.iron, TIBC, TSAT) p-value 0.701, 0.192, 0.382 respectively. Serum STfR was negatively correlated with s.iron in patients with CRP <10 mg/l (r -0.372, P 0.018).

Conclusion: Serum STfR is a sensitive and specific marker for iron deficiency anemia in hemodialysis patients, especially with high CRP.

Keywords: Soluble transferrin receptor,Iron deficiency,Anemia,Hemodialysis.

INTRODUCTION

Anemia is widely considered to be a significant consequence in hemodialysis (HD) patients, which negatively has an impact on patients' quality of life[1]. Among CKD patients, absolute iron deficiency is defined when the transferrin saturation (TSAT) is ≤20% and the serum ferritin concentration is ≤100 ng/mL among predialysis and peritoneal dialysis patients or ≤200 ng/mL among hemodialysis patients. Functional iron deficiency, also known as iron-restricted erythropoiesis, is characterized by TSAT ≤20% and elevated ferritin level[2]. There are several causes responsible for iron deficiency anemia in chronic hemodialysis patients. These include frequent laboratory testing, occult gastrointestinal bleeding, access bleeding, retention of blood in the dialysis tubing and dialyzers, decreased duodenal iron absorption (resulting from inflammation), interference with iron absorption (resulting from medications such as gastric acid inhibitors and phosphate binders), decreased iron-binding capacity resulting from a decreased concentration of transferrin[3] and supraphysiologic levels of erythropoiesis in the setting of erythropoietin-stimulating agents (ESA) therapy. Annual blood loss in this population can approximate 1.5 to 3 gm [4].

Exact estimation of the iron status in anemic patients who are on hemodialysis is difficult. There are many drawbacks of traditional laboratory biomarkers of iron status when used in hemodialysis patients[5], due to the inflammatory condition, which affects these markers and masks the iron deficiency.In recent years undergoing a revolution of new biomarkers.soluble transferrin receptor (sTfR) has been introduced as a sensitive, early, and valuable new marker of iron depletion not affected by inflammatory procedures and pathologic conditions[6]. This study evaluated the serum sTfR usefulness in iron deficiency anemia detection in prevalent hemodialysis patients.

PATIENTS AND METHODS

This case-control study was carried out on 80 ESRD patients on conventional HD with iron defciency anemia {serum hemoglobin< 12 gm/dl and transferrin staturation(TSAT <20%)}. Patients were divided according to c-reactive protein (CRP) into 2 equal groups matched as regards age and sex between 18 and 60 years old.group A: 40 ESRD patients with CRP>10 mg/l and group B: 40 ESRD patients with CRP<10 mg/l. Control group was 8 healthy subjects. all patients were on regular 3 sessions/week, each session 4 hours

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for at least 6 months with KT/V > 1.3 Excluding patients with catheter or graft, acute blood loss, recent blood transfusion or iron supplementation within 1 month, acute or chronic hepatic disease, active inflammation, or infection.

All patients were subjected to detailed history taking, clinical examination, complete blood count,red blood cell indices, iron profile {serum total iron, ferritin, total iron-binding capacity (TIBC), transferrin saturation (T.SAT)}, C-reactive protein (CRP), KT/V calculation, s.urea (pre-dialysis and post-dialysis), serum electrolytes {sodium (Na), potassium (k), calcium (ca), phosphorus (po4)} and PTH. Serum sTfR was measured with ELISA technique for all patients and controls.

Ethical consent:

An approval of the study was obtained from Ain Shams UniversityAcademic and Ethical Committee. Every patient signed an informed written consent for acceptance of the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Serum soluble transferrin receptor measurement:

Overall 4ml of venous blood samples was withdrawn. Serum was collected by serum separator tube, then was allowed to clot for 10-20 minutes at room temperature then centrifugation was done (at 2000-3000 RPM) for 20 minutes. Then supernatants were collected and stored at -20 ℃. Serum sTfR was measured by ELISA kit based on double-antibody sandwich enzyme-linked immunosorbent assay technology, shanghai crystal day biotech Co, LTD shanghai,china.

Statistical analysis:

Data were collected, revised, coded, and entered into the statistical package for the social science, version 20 (SPSS Inc., Chicago, Illinois, USA). The qualitative data were presented as numbers and percentages, whereas quantitative data were presented as mean with SD. Comparison between two groups with qualitative data was done by using the χ^2 Test. Comparison between two groups with quantitative data was done by two-tailed independent t-test when the distribution of the data was found parametric. Mann–Whitney test was used with the nonparametric data. Comparison between three groups with quantitative data was done by ANOVA with posthoc Tukey HSD Test when the distribution of the data was found parametric. Kruskal Wallis test was used with the nonparametric data. Spearman correlation coefficients were used to assess the correlations. P value ≤ 0.05 was considered significant.

RESULTS

Tables (1) showed the demographic and laboratory parameters for both HD patients with CRP<10 mg/l and CRP>10 mg/l. STfR can predict iron deficiency anemia in prevalent hemodialysis patients at the cut of value of 12.5 mg\l with area under curve (AUC) sensitivity of 88.75%, specificity of 100%, PPV100%, and NPV 47.1% (Figure 1). STfR was positive in 85% in patients with CRP<10 mg/l and 92.5% in patients with CRP>10 mg/l (P-value 0.288).

Table (2) showed a significant difference in comparing patients with CRP <10 mg/l, CRP >10 mg/l, and control as regards hemoglobin (Hb) and STFR with P-value 0.0001 and 0.0001 respectively. Post Hoc analysis showed a significant difference in comparing patients with CRP <10 mg/l with patients with CRP >10 mg/l in STfR p-value 0.0001. despite there was no significant difference as regards hemoglobin (p-value 0.642) and classic iron markers (s.iron, TIBC, TSAT) with p-value 0.701, 0.192, 0.382 respectively. (Table 1) serum STfR was negatively correlated with s.iron and Kt\v in patients with CRP <10 mg/l (r -0.372, P-value 0.018) and (r-0.416, p-value 0.008) respectively. There was no significant correlation observed between STfR and CRP in group A (CRP<10 mg/l) and group B (CRP>10 mg/l) with P-value 0.917 and 0.107 respectively.

Patients who had elevated STfR had a risk of 1.22 times to have iron deficiency anemia if CRP <10 mg/l (odds ratio: 1.22) and 3.14 times if CRP>10 mg/l (odds ratio: 3.14) (Table 3).

Table (1): Comparison between group A (CRP<10) and group B (CRP>10) as regard demographic & laboratory data

		Group A (CRP<10)	Group B (CRP>10)	P-value	Sig.
		No. = 40	No. = 40		
Sex	Male	23 (57.5%)	24 (60.0%)	0.820	NS
	Female	17 (42.5%)	16 (40.0%)		
Smoking	Smoker	6 (15.0%)	8 (20.0%)	0.556	NS
		Mean ± SD	Mean ± SD		
Age in years		43.50 ± 14.43	48.20 ± 12.72	0.126	NS
dose of ESA (IU per week)		10700 ± 2289.33	10400 ± 2687.10	0.592	NS
hemodialysis filter suface area (m^2)		1.63 ± 0.13	1.65 ± 0.12	0.419	NS
Weight (kg)		71.88 ± 7.61	70.93 ± 3.37	0.787	NS
dry wt (kg)		69.68 ± 7.49	68.73 ± 3.14	0.784	NS
interdialysis wt gain (kg)		2.20 ± 0.56	2.20 ± 0.65	1.000	NS
Hb (gm/dl)		8.88 ± 1.44	9.02 ± 1.19	0.637	NS
MCV (fl)		84.10 ± 7.30	84.75 ± 6.30	0.670	NS
MCH (pg)		27.38 ± 3.25	27.57 ± 2.61	0.782	NS
MCHC (%)		31.84 ± 2.97	32.35 ± 1.14	0.314	NS
WBCs(x10^9/L)		6.79 ± 1.79	6.86 ± 1.07	0.863	NS
platelets(x10^9/L)		225.78 ± 6.69	255.55 ± 9.64	0.072	NS
BUN(mg/dl)		28.34 ± 2.65	35.23 ± 2.41	0.016	S
Cr (mg/dl)		5.58 ± 1.01	5.69 ± 0.93	0.621	NS
Na(mEq/L)		136.38 ± 3.48	136.68 ± 1.51	0.618	NS
K (mEq/L)		5.19 ± 1.05	4.86 ± 1.16	0.185	NS
Ca (mg/dl)		8.78 ± 0.80	8.80 ± 0.81	0.912	NS
po4 (mg/dl)		4.48 ± 1.30	5.18 ± 1.25	0.017	S
kt/v		1.84 ± 0.2	2.21 ± 0.25	0.135	NS
s.iron (mcg/dl)		41.97 ± 5.83	41.24 ± 4.11	0.701	NS
TIBC (mcg/dl)		264.01 ± 9.75	246.77 ± 7.41	0.192	NS
TSAT (%)		16.07 ± 3.95	16.79 ± 3.29	0.382	NS
PTH(ng/l)		414.50±99.3	345±8.91	0.485	NS
URR(%)		0.71±0.14	0.7±0.13	0.776	NS
CRP(mg/l)		4.00 ±0.98	24±5.61	0.0001	HS
Duration of HD (months)		48.00 ±9.81	60 ±13.45	0.177	NS
Duration of ESA (months)		36.00 ±4.36	36 ±4.10	0.884	NS
S.Ferritin(ng/ml)		285.50 ±6.15	335.5 ±7.5	0.644	NS
STFRs(mg/l)		35.00 ±6.32	57.5 ±12.36	0.0001	HS

Table (2): Comparison between group A (CRP<10) and group B (CRP>10) and control group as regard hemoglobin, and STFRs.

	Group A (CRP<10)	Group B (CRP>10)	Control group	P-value	Sig.
	Mean ± SD	Mean ± SD	Mean ± SD		
Hb (gm/dl)	8.88 ± 1.44	9.02 ± 1.19	14.38 ± 1.53	0.0001	HS
STFRs (mg/l)	35±4.32	57.5±2.36	6.00±1.51	0.0001	HS
Post Hoc analysis by LSD					
	group A& control	group B & control	group A& B		
HB (gm/dl)	0.0001	0.0001	0.642		
STFRs (mg/l)	0.0001	0.0001	0.0001		

•: One Way ANOVA test; ‡: Kruskal Wallis test

Table(3): Logistic regression analysis for predictors of STFRs in Group A(CRP<10), and Group B (CRP>10)

	B	S.E.	Wald	P-value	Odds ratio (OR)		95% C.I. for OR				
							Lower		Upper		
STFRs (mg/l) In CRP<10	**0.203**	**0.087**	**5.489**	**0.019**	**1.225**		**1.034**		**1.451**		
STFRs (mg/l) In CRP>10					**1.144**	**0.178**	**1.697**	**0.193**	**3.140**	**0.561**	**17.562**

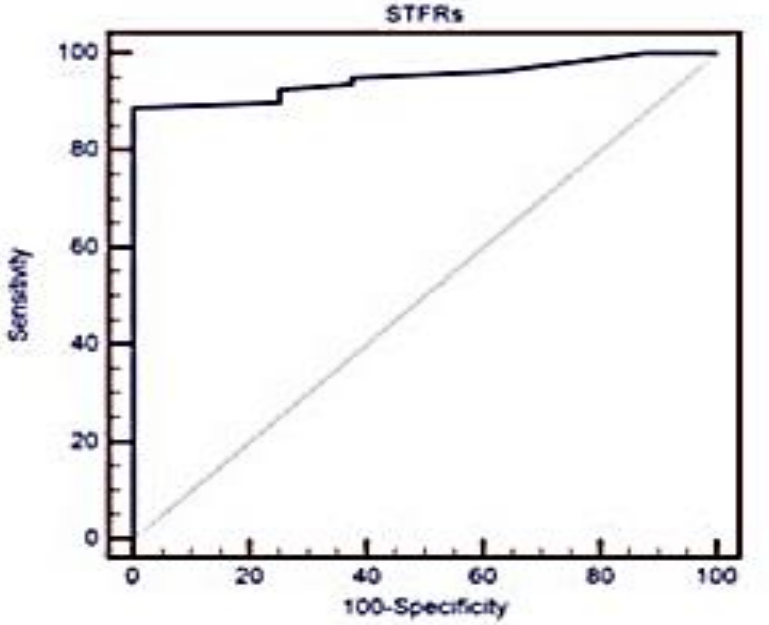

Figure (1): ROC curve of STfR in the prediction of iron deficiency anemia

DISCUSSION

The Exact estimation of iron status in anemic patients who are on hemodialysis is difficult [5].STfR measures the availability of iron in the bone marrow. It may be helpful to differentiate between anemia of chronic inflammation and iron deficiency anemia[7]. This study verified the usefulness of serum soluble transferrin receptors in iron deficiency anemia detection in prevalent hemodialysis patients. In this study the cut off value of STfR in hemodialysis patients was 12.5 mg/l with sensitivity of 88.75%, specificity of 100%, PPV of 100%, and NPV of 47.1%. This result agreed with **El-Gendy *et al.*** [8] who demonstrated that at a cutoff point of 5.45 mg/l sTfR has 80.9, 81.8, 63, 91.8, and 81.6% for sensitivity, specificity, PPV, NPV, and accuracy respectively for prediction of iron deficiency anemia.

Also, it agreed with **Shin *et al.*** [9] who found that the cut-off point for STfR was >2.30 mg/l with sensitivity of 85.4% and specificity of 91.9%. Also, our result agreed with **Gupta *et al.*** [10] in CKD patients where they found that the cut-off value of sTfR at its maximum sensitivity of 63.6% and specificity of 64.8% was 3 with a PPV of 59% and NPV of 69%. These differences in sensitivity and specificity in STfR may be due to the type of patients who were not hemodialysis patients. In our study STfR in the control group was 6 ±1.51 mg/l, this is near to the study that was done by **Alam *et al.*** [11] who found the mean of STfR was 7.31±1.81 mg/l, also **Shin *et al.*** [9] found very low median of STfR in the control group that was 1.14 mg/l.

In this study STfR in patients with iron deficiency anemia was positive in 85% of patients with CRP<10 mg/l and it was positive in 92.5% of patients with CRP>10mg/l. Patients who have elevated STfR have a risk of 1.22 times to have iron deficiency anemia if CRP <10 mg/l (odds ratio: 1.22) and 3.14 times if CRP>10 mg/l (odds ratio: 3.14). This agreed with **Gaweda**[12] who found that sTfR is not an acute-phase reactant and is less influenced by inflammation than other iron metabolism indices and the increased serum concentration of sTfR in hemodialysis patients is returned to iron deficiency rather than inflammation and it was inversely correlated with iron available for erythropoiesis as we found in our study in patients with CRP<10mg/l. it was negatively correlated with serum iron. There were no available studies with STfR odds ratio to compare with it.

The comparison between the patients in group A (with CRP<10 mg/l) and the patients in group B (with CRP >10 mg/l) showed no significant statistical difference as regards Hb and classic marker of iron deficiency. patients with CRP>10 mg/l had a higher level of STfR (mean ±SD 57.5 ±12.36 mg/l) in comparison with the patients with CRP<10 mg/l (mean ±SD 35.00 ±6.32 mg/l) with P-value <0.0001.despite no significant difference in the percentage of positive patients with STfR (p value 0.288) also There was no significant correlation observed between STfR and CRP

in group A (CRP<10 mg/l) and group B (CRP>10 mg/l) with P-value 0.917 and 0.107 respectively. So it was expressive for the iron status than classic iron markers in patients with inflammation. This was in agreement with **Suega*et al.*** [13] who found that there was no correlation observed between new iron indicators (sTfR, and Transferrin Receptor-Ferritin index) chosen with inflammation (CRP). Also, **Shin *et al.*** [9] found that ferritin had the strongest correlation with CRP, followed by TIBC and iron, whereas sTfR, hepcidin, and TSAT showed no correlation. So, classic iron markers (i.e., serum iron, TIBC, and ferritin) strongly have a vulnerability to inflammatory influence while the new marker sTfR was least influenced by inflammation. This was in disagreement with the study done by **Rohner *et al.*** [14] who found that concentrations of sTfR were weakly but positively associated with CRP, and it may be useful to assess iron-deficient erythropoiesis, but inflammation influenced its interpretation.

In patients with CRP<10 mg/l, there was a significant negative correlation between STfR level with serum iron with (r -0.372, P-value 0.018). This is in agreement with **Gupta *et al.*** [10] **and Belo *et al.*** [15] who found a significant negative correlation between STfR and S.iron (with $r = -0.447$ and $p < 0.001$) and($r = -0.445$; $P < 0.01$) respectively. Also the patients with CRP<10 mg/l had negative significant correlation between STfR and kt/v. This returned to adequate dialysis was associated with better hemoglobin and iron status as Dialysis therapy may directly affect bone marrow erythropoiesis by either removing substances that inhibit erythropoiesis, or by enhancing availability of iron[16].

CONCLUSION

We concluded that the Serum soluble transferrin receptor is a sensitive and specific marker for iron deficiency in hemodialysis patients especially in patients with high CRP levels.

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