Serum Erythroferrone, a Biomarker of Erythropoietic Activity in End-Stage Renal Disease Patients

Original Article

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ABSTRACT

Background: Hepcidin, a negative iron regulator, causes erythropoietin deficiency and reduced iron availability being the main cause of anaemia in chronic kidney disease (CKD). On the other hand, the erythropoietic stimulating agent inhibits hepcidin and increases the absorption and, mobilization of iron, stimulation of erythropoiesis, and curing anaemia through the production of erythroferrone. The research aimed to study the role of ERFE as a potential clinical biomarker for assessing erythropoiesis in end-stage renal disease (ERD) patients with iron deficiency anaemia.

Methods: Forty ERD patients (GFR < 15 ml/min/1.73 m2) with signs of iron deficiency anaemia were included in a case-control study. ERFE was assessed by ELISA both before and after iron/ESA treatment.

Result: The patient groups' ERFE levels were significantly different from the control group's either at baseline or following therapy (p=0.016 & 0.023, respectively). Patients receiving both iron and EPO had the greatest amount (212.31±106.33 ng/L at baseline and 520.00±255.26 post-treatment). It was shown that there was a positive correlation (p-*value* <0.05) between the ERFE level and serum iron and hemoglobin.

Conclusion: To manage anaemia in ESRD patients, it is worth creating new diagnostic and therapeutic techniques by understanding iron homeostasis. The link between ERFE and iron/EPO therapy as well as its positive correlation with hemoglobin and blood iron levels was established. Thus, ERFE may have a significant impact on the management of patients with iron deficiency as well as the evaluation of erythropoietic function.

Key Words: Chronic kidney disease, end-stage renal disease, erythroferrone, iron.

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INTRODUCTION

The aetiology of anaemia in people with chronic kidney disease (CKD) is mostly attributed to disruptions in iron homeostasis and inflammation. Thus, iron supplements and erythropoiesis-stimulating agents (ESA) are currently used to promote erythropoiesis[1].

In 2012, Bamgbola denoted that iron deficiency or impairment of iron availability is the most common cause of recombinant human erythropoietin (rHu EPO) treatment resistance[2]. Furthermore, there are urgent clinical issues due to ESAs' hypo responsiveness and their unfavorable clinical outcomes (myocardial infarction, congestive heart failure, and mortality)[3, 4]. As a result, novel treatment approaches for CKD-related anaemia should be looked into.

The protein ferroportin imports iron via duodenal enterocytes into the plasma. Moreover, it releases recycled iron from macrophages, as well as stored iron from hepatocytes to plasma. Hepcidin binds to ferroportin and negatively regulates plasma iron levels[5,6] .A major contributing factor to functional iron shortage in CKD patients is the chronically inappropriate rise of hepcidin concentration brought on by impaired renal clearance and inflammatory upregulation. Thus, contributing to suboptimal response to ESAs with inappropriate escalation of ESAs doses[7].

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Erythroferrone (ERFE), a hormone produced in erythroblasts during stress erythropoiesis (during rapid growth or blood loss), directly inhibits the expression of hepcidin, accompanied by an increase in the cellular iron export channel ferroportin[8]. Its expression rises upon EPO injection or endogenously created as well as following phlebotomy and is dependent on the activity of the signal transducer and activator of transcription 5 factor (STAT5)[9]. Additionally, a dose-response association between the amount of ESAs provided and circulating ERFE was observed[10]. Thus, ERFE could be a useful biological marker of iron metabolism and a therapeutic target, playing a role in the recovery from anaemias with ineffective erythropoiesis either inherited or acquired.

Our research focused on the associations between ERFE levels and iron indicators, as well as the responsiveness to therapy in end-stage renal disease (ERD) patients.

SUBJECTS AND METHODS

Subjects

This prospective case-control study was conducted onpatients with ERD, attending the Internal Medicine and Nephrology Unit of Ain Shams University Hospitalsduring the period from January 2018 to June 2018. The diagnosis was based on GFR <15 ml/min/1.73m². Both dialyzed and non-dialyzed patients displaying signs of iron-deficiency anaemia were includedin the study. Patients were further subdivided into 2 subgroups according to the Kidney Disease Global Outcomes (KDIGO,2012) guidelines which indicate that ESA should not be started in patients with Hb level > 10g/dl[4].

Subgroup I consisted of 28 patients with Hb level <10 g/dl who got both iron and ESAs and subgroup II consisted of 12 patients with Hb level >10 g/dl who were treated exclusively with iron.

Patients with non-renal causes of anaemia other than iron deficiency, as well as those who received a blood transfusion within the former 4 months, and patients with evidence of active bleeding or active infection requiring antibiotics within the former 4 weeks were excluded.

Ten apparently healthy participants with matched age and gender to patients were included in the study as a control group.

The number of patients (n =40) included in the study was recommended by the medical statistical center at Ain Shams University.

Ethical Consent

All enrolled subjects provided written informed consent. The Ain Shams University Scientific and Ethical Committee accepted the study, and as per the declaration of Helsinki.

Initial assessment

Full history and thorough clinical examination, laying stress on age, sex, dry weight, duration of dialysis, and presence of comorbidities were applied.

Laboratory investigations were done at the baseline of the study and then re-evaluated 3 months later after iron ± ESA therapy.

Sampling

Ten millilitres of peripheral patients' blood samples were collected before the mid-week haemodialysis session and before heparin administration.

Two ml were collected in EDTA vacutainer tube for CBC and the remaining of blood was collected into 2 different plain tubes for performing the chemistry and serological tests, as well as measuring the ERFE level.

Allow serum to clot for 10-20 minutes at room temperature, then centrifuged at 2000-3000 RPM for 20 minutes. The serum was separated and stored at -20°c until used for performing the chemistry and serological tests, as well as measuring the ERFE level.

Laboratory tests

The CBC was performed using Sysmex XS500i,a 5-part differential analysis (Sysmex Corporation, Kobe, Japan). Serum iron level, serum transferrin saturation, and CRP titre were analyzed using AU480 (Coulter, Electronics, Hialeah, FL, USA).

Erythroferrone level

Serum erythroferrone was performed by Enzyme-Linked Immunosorbent Assay (ELISA), using the Human

Erythroferrone ELISA Kit "Human Protein FAM132B ELISA KIT", Catalogue No: E3957Hu, Bioassay Laboratory Technology, China. The detection range was from 5-1500 ng / L, with sensitivity up to 2.4ng / L.

The principle of the ELISA technique dependson the binding of FAM132B present in the sample to the pre-coated plate with the FAM132B antibody. Then the biotinylated human FAM132 antibody is added and binds to FAM132B in the sample, which in turn binds to the added Streptavidin-HRP. After incubation, unbound Streptavidin-HRP is washed away during a washing step. A color develops in proportion to the amount of human FAM132B present in the sample upon adding the substrate solution. Finally, the acidic acid stop solution is used to terminate the reaction and read the absorbance at 450 nm.

Statistical analysis

Data were analyzed using Statistical Package for Social Science (IBM SPSS) version 20. Numbers and percentages present qualitative data. On the other hand, mean and standard deviation were used to represent parametric quantitative variables, whereas median and interquartile range were used to represent non-parametric ones. (IQR; the difference between 25^{th} and 75^{th} centiles).

When comparing two groups based on qualitative data, the Chi-square test (X2) was employed; however, when the predicted count in any cell was less than 5, the Fisher exact test took its place. As regards the quantitative parametric data, an independent t-test was performed. In contrast, two groups with non-parametric quantitative distributions were compared using the Mann-Whitney test. Lastly, to compare related samples, a paired sample t-test of significance was used.

Pearson's correlation coefficient (r) test was used to assess the degree of association between 2 sets of variables. Mean difference (difference between second and first reading) and percentage change (difference between second and first reading/first reading x 100) were used to determine the mean improvement following the intervention.

In every analysis, a *p-value* of less than 0.05 was deemed to be the threshold for significance.

RESULTS

(Table 1) includes clinical and demographic information about the patients.Forty ESRD patients with a male-to-female ratio of 1:1.5 participated in the current study. Theirmeanage and dry weight were 51.03±11.22years and 73.4±13.08 Kg respectively. Hypertension was the most common risk factor, accounting for 32.5% of cases.

No significant statistical difference at baseline between both patients' subgroups as regards all demographic, clinical, and laboratory data except for hemoglobin (Hb) and haematocrit (HCT) as those treated with iron only (subgroup II) had higher levels (p<0.001) (Data not shown). In contrast, TIBC was lower in subgroup II and significantly different after iron therapy.

The control group had a male-to-female ratio of 1and a mean age of 51.4±12.35, matching the patient group's age and sex (p= 0.927 & 0.943, respectively).

The comparison between baseline and post-treatment laboratory data in subgroup I, revealed a significant increase in Hb level, HCT, serum iron, and transferrin saturation percentage (TSAT %) (p < 0.001), with a decrease in total iron-binding capacity (TIBC) (p = 0.047).

Similar results were obtained upon comparing the baseline and post-treatment laboratory data in subgroup II except that despite the increase in HCT & decrease in TIBC, their changes were insignificant.

Table 1: Patients' demographic, clinical, and laboratory data.

			All patients (*n*=40)	Subgroup I Treatment with iron + erythropoietin (*n*=28)	Subgroup II Treatment with iron (*n*=12)
Age (years)	Mean ± SD		51.03±11.22	49.96±12.05	54.11±8.15
Sex	Female n (%)		24 (60%)	17 (60.7%)	7 (58.3%)
	Male n (%)		16 (40%)	11 (39.3%)	5 (41.7%)
Dry weight (Kg)	Mean ± SD		73.40±13.08	71.50±12.93	78.89±12.58
HCV Positive	n (%)		10 (25%)	5 (17.9%)	5 (41.7%)
Hypertensive Patients	n (%)		13 (32.5%)	10 (35.7%)	3 (25.0%)
Diabetic Patients	n (%)		7 (17.5%)	4 (14.3%)	3 (41.7%)
CRP titre	Mean ± SD		7.35±2.54	7.62±2.71	6.67±2.00
Hb (g/dl)	Mean ± SD	Baseline	8.88±1.27	8.37±1.05	10.34±0.41
		Post-treatment	10.46±1.27	10.04±1.18	11.69±0.50
HCT %	Mean ± SD	Baseline	27.40±4.56	25.57±3.64	32.70±2.12
		Post-treatment	31.43±3.71	30.18±3.34	35.03±1.96
MCV (fl)	Mean ± SD	Baseline	79.25±5.36	79.01±6.05	79.95±2.57
		Post-treatment	80.06±5.78	79.17±5.92	82.63±5.73
MCH (pg)	Mean ± SD	Baseline	25.87±2.15	25.96±2.45	25.59±0.82
		Post-treatment	26.64±2.21	26.30±2.28	27.62±1.74
Serum iron (µg/dl)	Mean ± SD	Baseline	34.46±8.25	35.12±8.96	32.56±5.77
		Post-treatment	51.57±13.86	51.92±14.30	50.56±13.25
TIBC (µg/dl)	Mean ± SD	Baseline	241.11±56.33	250.23±56.80	214.78±48.53
		Post-treatment	218.97±32.44	226.85±29.76	196.22±30.34
TSAT %	Mean ± SD	Baseline	14.49±3.47	14.21±3.51	15.30±3.45
		Post-treatment	23.77±5.98	23.13±5.89	25.61±6.21
Erythroferrone (ng/L)	Mean ± SD	Baseline	202.00±102.69	212.31±106.33	172.22±90.25
		Post-treatment	504.29±236.36	520.00±255.26	458.89±175.17

HCV: Hepatitis C Virus; DM: Diabetes Mellitus; CRP titre: C-reactive protein; Hb(g/dl): Haemoglobin; HCT%: Haematocrit; MCV (fl): Mean corpuscular volume; MCH (pg): Mean corpuscular haematocrit; TIBC(µg/dl): Total iron-binding capacity; TSAT%: Transferrin saturation.

Erythroferrone level

Before therapy, the ERFE level was significantly increased in all ERD patients (202.69±102.69 ng/L) (p=0.016) compared to the control group. After therapy, its level was significantly higher among the patients (504.29±236.36 ng/L) than controls (p<0.001) (Table 2).

On comparing both patient subgroups to control and to each other, the ERFE level was significantly increased in the group that received iron only (group I) (172.22±90.25 ng/L) and the group that received iron+ EPO (group II) (212.31±106.33 ng/L) compared to controls (p=0.023 & p<0.001) respectively. However, no significant difference was detected between both patients' subgroups, neither at baseline nor post-treatment as regards ERFE level (Table 3).

Also, post-treatment ERFE level showed a highly significant difference upon comparing the control group with all patients and with both patients' subgroups (p < 0.001), with the highest level in subgroup I (520.00±255.26 ng/L) (Table 2 & 3).

Table 2: Comparison of erythroferrone level between the control group and all patients.

		Control Group (*n*=10)	Patients (*n*=40)	z-test	*p-value*
Baseline Erythroferrone (ng/L)	Mean ± SD	115.00±40.14	202.69±102.69	2.657	0.016*

Using; z-Mann-Whitney test; **p-value* <0.05 S; ***p-value* <0.001 HS.

Table 3: Comparison of erythroferrone level between the control group and patients' subgroups

		Control Group (*n*=10)	subgroup I: (Treatment with iron & erythropoietin) (*n*=28)	subgroup II: Treatment with iron only) (*n*=12)	z-test	*p-value*
Baseline Erythroferrone (ng/L)	Mean ± SD	115.00±40.14**B**	212.31±106.33**A**	172.22±90.25**A**	5.648	0.023*
Post-treatment Erythroferrone (ng/L)	Mean ± SD	115.00±40.14**B**	520.00±255.26**A**	458.89±175.17**A**	17.683	<0.001**

Using: H-Kruskal Wallis test; **p-value* <0.05 S; ***p-value* <0.001 HS
Values in each row that have different letters are significantly different at (*P*<0.05).
At baseline: Control vs. subgroup I (*p*=0.017*); Control vs. subgroup II (*p*=0.039*)
Post-treatment: Control vs. subgroup I (*p*=<0.001); Control vs. subgroup II (*p*=<0.001)

No significant difference was detected between both patients' subgroups, neither at baseline nor posttreatment as regards ERFE level.

On the other hand, the comparison of each subgroup separately showed a significant statistical difference between its baseline, post-treatment, and delta change of the ERFE level (subgroup I: $p < 0.001$; subgroup II: p=0.004) (Figure 1 & 2).

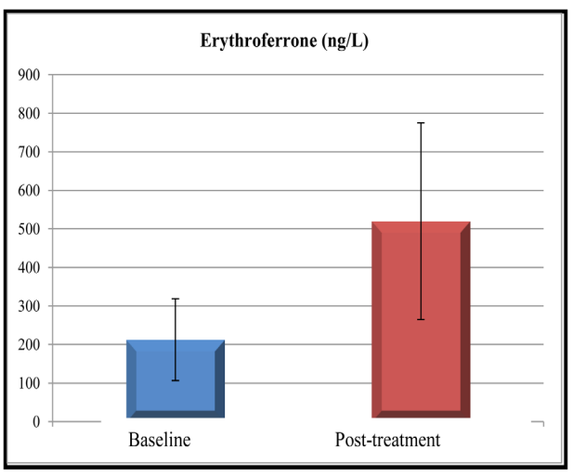

Fig. 1: Comparison between Baseline and Post-treatment Erythroferrone level (ng/L) in Subgroup I.

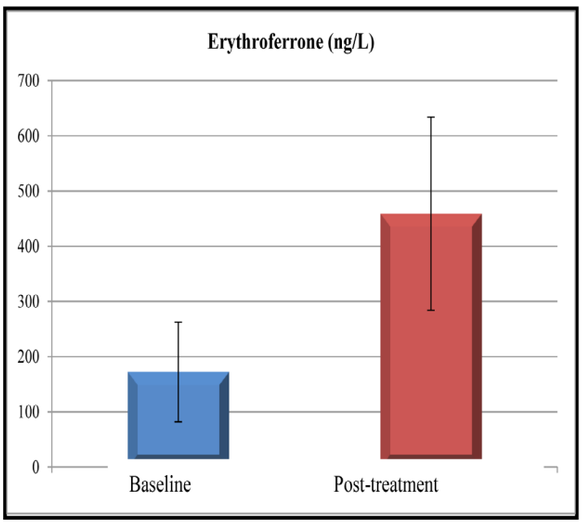

Fig. 2: Comparison between Baseline and Post-treatment Erythroferrone level (ng/L) in Subgroup II.

Finally, a positive correlationwas found between ERFE level and both of Hb level and serum iron level either at baseline assessment or after treatment in the two patient subgroups ($p < 0.05$) (Figure 3 & 4).

It is of interest to denote that there was no noticeable distinction when comparing the level of ERFE in each patient's subgroup with the presence or absence of different comorbidities (HCV infection, hypertension, and diabetes).

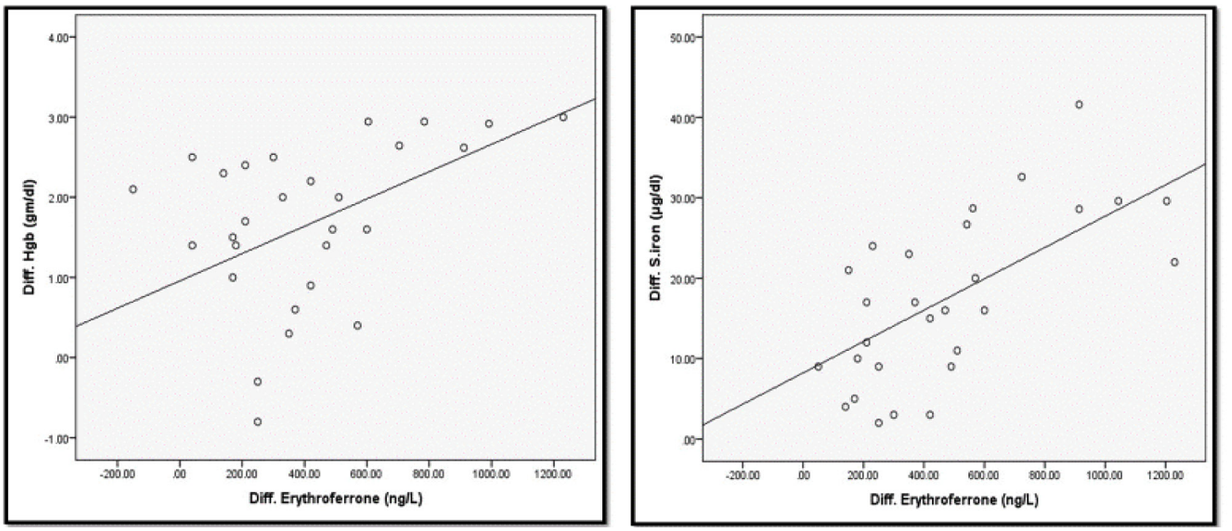

Fig. 3: Scatter plot between delta change in Erythroferrone (ng/L) with delta change in Hb (g/dl) and Serum Iron (µg/dl) in subgroup I.

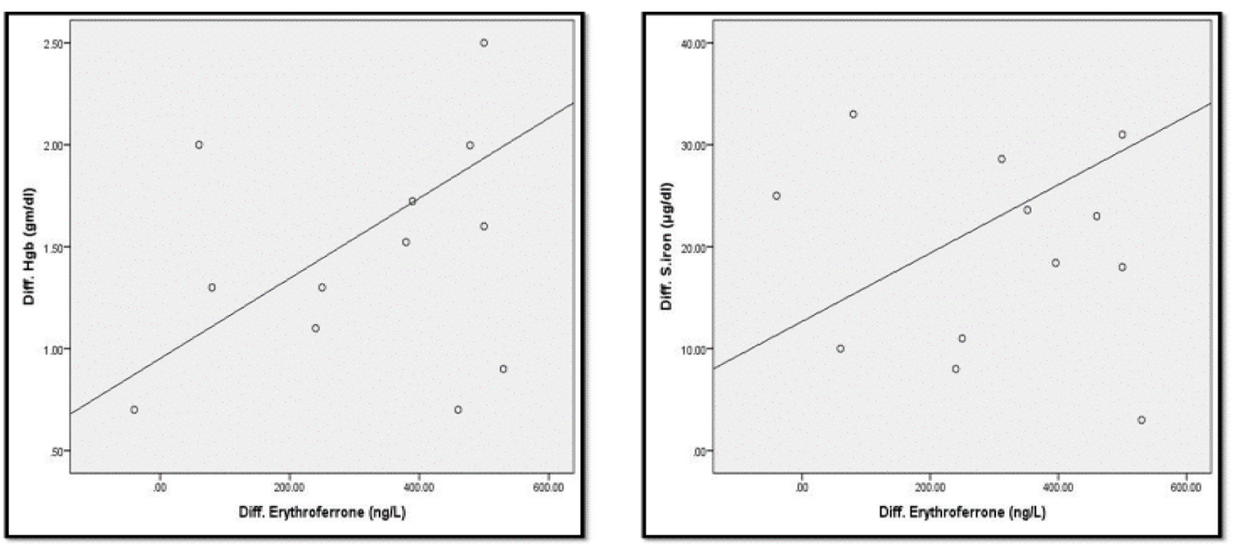

Fig. 4: Scatter plot between delta change in Erythroferrone (ng/L) with delta change in Hb (g/dl) and Serum Iron (µg/dl) in subgroup II.

DISCUSSION

Anaemia is a vulnerable complication of CKD, present in 69.4% of patients[11], and the most frequent causes are erythropoietin and iron insufficiency. As, iron deficiency, being independent of potential cofounders, influences morbidity and mortality. Thus, it is of utmost importance to understand how CKD affects iron homeostasis control and disruption, to discover new diagnostic and therapeutic tools, and subsequently improve anaemia[12].

The hepcidin-feroportin axis is crucial for controlling the iron balance in the body. In 2014, ERFE was identified in mice,it is produced by erythroblasts in response to EPO and it inhibits hepcidin production through its direct action on the liver[13]. Since its discovery and till now, there have not been enough studies of ERFE among humans. So, to shed light on the ERFE concentrations and their correlation with different iron parameters, we chose to do the study on 40 ESRD patients, who suffered from iron deficiency anaemia and received either iron supplement only or combined iron and EPO therapy.

Our patients' mean age was 51.03±11.22 years with a male-to-female ratio of 1:1.5. and mean dry weight 73.4±13.08 Kg. The commonest risk factor was hypertension (32.5%). Similar results were denoted by ***Pretto et al.*** who conducted a cross-sectional study with 183 patients with CKD, 55.2% of whom were 60 years of age or older, and 35.0 % were hypertensive[11].

The higher level of Hb and HCT in subgroup II patients (those receiving iron supplement only) than those patients in subgroup I (those receiving combined iron supplement and EPO) goes with the Kidney Disease Global Outcomes (KDIGO,2012) guidelines which indicates that ESA should not be started in patients with Hb level > 10g/dl[4].

Higher levels of baseline ERFE were detected among patients' groups (202.69±102.69 ng/L) compared to the control group (115.00±40.14 ng/L), and the highest level was in those treated with both iron and EPO (212.31±106.33 ng/L). This was consistent with the findings of ***El Gendy et al.***, who reported that serum ERFE levels in individuals with iron deficiency anaemia were notably greater than those in the control group[14]. Moreover, ***Hanudel et al.*** demonstrated that dialyzed patients had higher serum ERFE levels than the healthy subjects[15]. ***Saad et al.*** demonstrated a significant increase in ERFE in ß thalassemia patients compared to a control group[16]. Lastly, cases withanaemia due to malarial infection had noticeably greater ERFE levels than asymptomatic controls[17].

In contrast to our study, ***Honda et al.*** found that the ERFE level in 59 haemodialysis patients did not differ from those of control subjects with normal kidney function. This could be attributed to the use of a different assay with different characteristics to that of the human assay and it was not validated in physiological or pathological conditions that would be expected to have elevated ERFE levels[18]. The same findings were shown by Dulkadir and his co-workersas no significant difference in serum ERFE levels between the control group and the iron deficiency group was denoted, also ERFE levels remained unchanged after iron deficiency treatment. This is believed to be related to the brief course of iron therapy that the study's iron-deficient anaemia patients received[19].

Following iron supplements and/ or EPO therapy, ERFE levels increased with statistically significant difference upon comparing with the control group ($p < 0.001$) and following the comparison between baseline and post-treatment ERFE level in each patient's subgroups (subgroup I: $p < 0.001$; subgroup II: $p=0.004$). The highest ERFE level was found in the subgroup I treated with both iron and EPO (520.00±255.26 ng/L). In agreement with our results, ***Cuevas et al.*** proved that blood ERFE levels increased up to 8 folds after injection of various ESAs[20]. Moreover, ***Robach et al.*** demonstrated that in healthy humans, ERFE was promptly enhanced in response to moderately increased EPO levels[21].

Furthermore, a positive correlation between ERFE level and both Hb level and serum iron level either at baseline assessment or following treatment in both patients' subgroups ($p < 0.05$) was declared. This correlation reinforces the theory thathepcidin expression is directly inhibited by ERFE, while ferroportin, the cellular iron export channel, is upregulated in tandem.This is consistent with the results of ***Hara et al.*** studyand ***Saad et al.*** and in disagreement with ***Spoto et al.*** [22, 16, 12]. Further research is necessary to clarify this controversy and demonstrate how ERFE modulates iron homeostasis and how useful it is as a biomarker for efficient erythropoiesis in individuals with CKD.

CONCLUSION

A key to creating novel treatment approaches that enhance the management of anaemia (one of the most prevalent characteristics of CKD) is comprehending the process underlying iron balance dysregulation in CKD patients. Given the substantial variation in serum ERFE levels between the iron deficiency group and the control group, it is plausible that ERFE regulates iron metabolism and could be utilized as a biomarker of erythropoietic activity and EPO responsiveness in CKD- related anaemia.

COMPETING INTEREST

There are no conflicts of interest is declared by authors.

DECLARATION

The paper is not under consideration elsewhere, and none of the paper's contents have been previously published.

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الإريثروفيرون: علامة حيوية لنشاط كريات الدم الحمراء في مرضى المرحلة النهائية للفشل الكلوي

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[٣]وزاره الصحه و السكان، مصر

الخلفية: يسبب الهيبسيدين، وهو منظم سلبي للحديد، نقص الإريثروبويتين وانخفاض توافر الحديد كونه السبب الرئيسي لفقر الدم في مرض الكلى المزمن. من ناحية أخرى، فإن عامل تحفيز كريات الدم الحمراء يثبط الهيبسيدين ويزيد من امتصاص الحديد، وتحفيز الكريات، وعلاج فقر الدم من خلال إنتاج الإريثروفرون. يهدف البحث إلى دراسة دور ERFE كمؤشر حيوي سريري محتمل لتقييم تكون كريات الدم الحمراء في مرضى أمراض الكلى في المرحلة النهائية الذين يعانون من فقر الدم الناجم عن نقص الحديد.

الطريقة: تم تضمين أربعين مريضا ب ESRD (GFR < ١٥ مل / دقيقة / ١,٧٣ م ٢) مع علامات فقر الدم الناجم عن نقص الحديد في دراسة الحالات والشواهد. تم قياسERFE بواسطة ELISA قبل وبعد العلاج بالحديد / ESA.

النتيجة: كانت مستويات ERFE لمجموعات المرضى مختلفة بشكل كبير عن المجموعة الضابطة إما قبل أو بعد العلاج (p = ٠,٠١٦ و٠,٠٢٣، على التوالي). وكان لدى المرضى الذين يتلقون كلا من الحديد وEPO أكبر كمية (٢١٢,٣١±١٠٦,٣٣ نانوغرام / لتر قبل العلاجو ٥٢٠,٠٠±٢٥٥,٢٦ بعد العلاج). وقد تبين أن هناك علاقة إيجابية (قيمة p <٠,٠٥) بين مستوى ERFE وحديد المصل والهيموجلوبين.

الخلاصة: لإدارة فقر الدم لدى مرضى ESRD، يجدر إنشاء تقنيات تشخيصية وعلاجية جديدة من خلال فهم توازن الحديد. بناءا على العلاقة بين ERFE والعلاج بالحديد / EPO بالإضافة إلى ارتباطه الإيجابي بالهيموجلوبين ومستويات الحديد في الدم، قد يكون ل ERFE تأثير كبير على متابعة المرضى الذين يعانون من نقص الحديد وكذلك تقييم وظيفة كريات الدم الحمراء.

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