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Prevalence of Functional Iron Deficiency (FID) Anemia in Patients Undergoing Hemodialysis

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ABSTRACT

Aims: Anemia is one of the main problems in hemodialysis patients, which is caused by inadequate production of erythropoietin. Functional iron deficiency (FID) anemia is a kind of anemia, which lack of functional iron therein leads to resistance and inappropriate response to erythropoietin in hemodialysis patients. Since early diagnosis of this anemia before erythropoietin usage is important, this study was conducted "to determine prevalence of functional iron deficiency in hemodialysis patients".

Methods: In a cross–sectional design studied 184 patients with chronic kidney disease referred to hemodialysis units in Baqiyatallah and Chamran hospitals in Tehran. In order to data collecting were measured serum Hb, Hct and Ferritin levels plus to completing the demographic questionnaire. The χ^2-test, T-test and ANOVA were used in this study. The data were analyzed via the $SPSS_{18}$ software (version). The p value of 0.05 was considered as significance level.

Results: The mean of serum levels of Hb and Hct was respectively 10.98±1.7 g/dl and 34.1±5.2%. Anemia was observed in 37%, hyperferritinemia in 80.4% and functional iron deficiency anemia in 41.1% of patients.

Conclusions: Functional iron deficiency was observed in about half of hemodialysis patients and could cause resistance and inappropriate response to Erythropoetin in them. Therefore nurse awareness and his/her duly action in determining the status of iron stores prior to the administration of erythropoietin prevents from prescribing an expensive drug and imposing unnecessary costs to the patient and the health care system.

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1. Introduction

One of the main complications of chronic kidney disease (CKD) is anemia [1] which creates mainly by kidney weakness in producing erythropoietin and also iron deficiency [2]. Renal anemia is intensified in intermediate stage of chronic renal failure and exacerbates in parallel with the development of renal failure [3].

Anemia can lead to cardiovascular disorders, cardiomyopathy and increase in the risk cardiovascular mortality in hemodialysis

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patients [4-5]. Also the severity of anemia in these patients is in relation with increased risk of hospitalization, morbidity and considerable decrease in the quality of life (QOL) [6-7].

Up to 15 years ago, the main treatment for anemia in hemodialysis patients was blood transfusion, despite all associated risks [8]. But in 1989, recombinant human erythropoietin (rHuEpo) became available for patients [9]. Erythropoietin is an effective and well-tolerated treatment with documented clinical benefits [1] whose administration is advised if hemoglobin and hematocrit been respectively less than 10-11g/dL and 30% [10].

Different factors affect on the efficiency of erythropoietin and the most important of them is the sufficiency of functional iron stores. Ferritin is the main protein of iron storing in the blood and its normal serum amount is a good indicator for investigating the available iron stores [11]. For this reason, serum ferritin measuring is the best indicator for iron stores monitoring in CKD patients [12].

Sometimes, incomplete metabolism of iron (deficiency in iron, applying) even in the presence of enough stores causes an inappropriate response to erythropoietin, which is called functional iron deficiency (FID) [13-15]. This anemia is diagnosed with serum hemoglobin less than 11 gr/dl and ferritin more than 200 ng/dL. Deficiency in iron metabolism related to chronic inflammation is very common in CKD patients due to inflammation mediators releasing in chronic renal failure, hemodialysis process, loss of B12 vitamin or fulat and increase in oxidative stress [16].

Increase in serum ferritin (hyperferritinemia) in these patients can be a sign of hemochromatosis, haemosiderosis or iron toxicity [17]. Early diagnosis and treatment of this anemia in hemodialysis patients causes a decrease in left ventricular hypertrophy and its morbidity and mortality [8-9], an increase in the power of activity tolerance in daily life and the quality of life improvement [18].

Dialysis nurses have a unique and exceptional role in timely diagnosing and managing anemia in hemodialysis patients. These nurses can investigate and manage iron deficiency before erythropoietin usage via careful investigation of patients' complaints, signs, experiments and medicines and prevent from the useless prescription of this expensive medicine [12].

Limited studies have been conducted up to now on functional iron deficiency anemia in hemodialysis patients [19]. On the other hand, timely diagnosis of this anemia in these patients can have a considerable effect on better use of erythropoietin [13]. The aim of this study was to "investigate the frequency of functional iron deficiency anemia in hemodialysis patients".

2. Methods

This study was directed from October 2012 to January 2013 by using a descriptive cross-sectional design on 184 patients receiving maintenance dialysis in two hemodialysis units in Baqiyatallah and Chamran hospitals of Tehran, Iran. The sampling frame included all ESRD patients who were older than 18 years, regular recourse for maintenance hemodialysis two or three sessions per week, receiving dialysis for≥3 months, lack of history of major surgery from six months ago, being infected by active infections, getting cancers, smoking and passive smoke exposure, and alcohol consumption.

Prior ethical approval was obtained from the institutional ethical committee at the Baqiyatallah University of Medical Sciences, Tehran, Iran. A justification letter was sent to two hemodialysis units and permission obtained to collect data granted by these units. For all those who participated in the study verbal and written consents were obtained. Written consents were obtained after informing each participant about the study purposes, the "confidentiality" of their information, and the possibility to refuse the test procedure at any stage of it.

The research instrument consisted of two parts; a demographic questionnaire and a checklist of laboratory parameters. A demographic questionnaire was developed by the researcher

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to record age, gender, marital and education status, number of children, employment status, income, weight, smoking history, nephropathy cause, and length of time receiving dialysis. Serum levels of Hb, Hct and Ferritin also were measured.

In the beginning, 5 ml venous blood sample was obtained from the subjects. Then 1.5 mL of this blood sample was poured into tubes containing ethylene diamine tetra acid for measuring hemoglobin and hematocrit respectively by Spectrophotometer device (LKB, UK) and Microhematocrite (Made in Germany) and 3.5 mL into door pull tubes without ethylene diamine tetra acid for measuring ferritin by Gamacounter device (Finland, Contron) with RIA method, using kits (Merck, Germany). 98.9% of patients received recombinant human erythropoietin (Eprex 2000 U of Cilag factory) with a mean dose 57.5±22.5 IU/ kg /week.

In accordance with the National Kidney Foundation of America, anemia was diagnosed with hemoglobin less than 11g/dL and hematocrit less than 33%. Ferritin greater than 200 ng/mL was considered as hyperferritinemia. According to the NKF-K/DOQI Guideline also laboratory indicators of serum hemoglobin less than 11 g/dl and ferritin greater than 200 ng/ml together, was interpreted as functional iron deficiency [6].

The data were analyzed by version 18 SPSS software. The $\chi 2$-test, T-test and ANOVA were used. The significance level was put at 0.05.

3. Results

This study included 184 hemodialysis patients with a mean (standard deviation) age 61.67±12.56. The mean age of males was 61.7±13.1 and women were 61.6±11.9. The mean of dialysis vintage was 37.6 ±42.25 months. The most common underlying causes of nephropathy were respectively hypertension and diabetes (hypertension 36%, diabetes 14%, and 29% for both). Other demographic data are

Table 1: Demographic characteristics of the participants

Characteristic (n=184)	Frequency N (%)
Gender	
female	70 (38)
male	114 (62)
Education	
Primary	78 (42.4)
Under diploma	18 (9.8)
Diploma	52 (28.2)
University	36 (19.6)
Nephropathy cause	
HTN	67 (36.4)
DM	25 (13.6)
Glomerulonephritis	6 (3.3)
HTN and DM	54 (29.3)
Others	32 (17.4)
Marital	
Maried	155 (84.2)
Singel	5 (2.7)
Widow	24 (13.1)
Occupation	
Unemployed, housekeeper	73 (39.6)
Employed	15 (8.2)
Retired	96 (52.2)

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reported in Tables 1 and 2.

Anemia was observed in 68 patients (37%), hyperferritinemia (ferritin more than 200 ng/ml) 148 patients (80.4%) and functional iron deficiency in 76 patients (41.3%). Although the mean of Hb and Hct in women were less than males, but it did not reach to significant levels (p=0.07) (Table 3). There was a significant relationship between hyperferritinemia and dialysis vintage (p=0.01). The details are showed at table 4. Serum levels of Hb and Hct in patients with a history of hospitalization in the two months ago was less than other patients (p=0.02, p=0.006) (Table 5). Data analysis showed a significant association between education level and income levels (Tables 6 and 7).

4. Discussion

The results of this study showed that functional iron deficiency anemia is very common among hemodialysis patients.

The major part of the total 184 subjects of this study was males. In the studies of Hojjat [20], Medanloo [21], Farahani [22], Tayebi [23], Nazemian [24] and Savari [25], most of the subjects were males too. This point and finding of reason of increase of prevalence and incidence of chronic renal failure in males can be a research appropriate field.

According to the result of the previous studies, the frequency of CKD in people over 45 is higher and this matter confirms the results of this study [26].

Based on the results of Nabipoor's study, high blood pressure (75.5%) and diabetes (21.4%) are the most common background diseases in patients with cerebrovascular accident (CVA) and myocardial infarction (MI) [27].

In our study also, these two illnesses are known as the most common causes of nephropathy. The mean of hemoglobin obtained in this study is similar to studies conducted in two recent years like Lovcic (2011) [28], Lukic (2012) [29], Emami (2012) [30] and Sajjadi (2013) [31]. But serum hemoglobin reported in studies conducted in the last decade, like Jungers (2002) [3], Rahimian (2005) [32], Shahidi (2002) [33] and Kashi (2006) [34], was lower that it can be a sign for improvement of anemia treatment status and hemodialysis techniques in recent years.

Also the frequency of anemia was lower in this study compared to Jungers (2002) [3], Sharifian (2002) [35] and Afshar (2009) [2]. This can be due to appropriate treatment of anemia in recent years.

But in comparison with McClellan [14], the frequency of anemia is higher in this study, and its cause can be related to our patients' resistance to erythropoietin.

A study in Spain [36] on 4333 hemodialysis patients showed that 60 percent of the patients were affected by absolute and functional iron deficiency anemia (39 percent had absolute iron deficiency and 21 percent had a functional iron deficiency). A study in Iran also reported the prevalence of absolute and functional iron

Table 2: Baseline quantitative characteristics of the respondents

Variables	Mean±SD
Age, year	61.67±12.6
Dialysis vintage, month	37.6±42.2
Body weight, Kg	69.3±11.6
Serum parameters	
Hb, g/dL	10.98±1.7
Hct, %	34.1±5.2
Ferritin, ng/ml	620.8±577.7
RDW,%	14.46±2.2

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deficiency anemia respectively 11 and 24 percent.

Functional iron deficiency anemia was more prevalent in the present study compared with two mentioned studies. Maybe more prescription of injective iron in our patients, the presence of effective factors on transferrin saturation (such as excretion of transferrin via the kidneys) and also chronic inflammation derived from hemodialysis and using some non high Flux hemodialysis filters be the reason for this matter.

The mean of the serum ferritin in this study was more than some similar studies (Lovcic and Afshar) and also iron mean reported in nondialysis renal patients [29] that can be due to more prescription of injective iron, lack of self-adjusting in iron use, chronic inflammation, and higher resistance to erythropoietin in our patients [37-38].

According to the results of the present study, the prevalence of anemia in Iran is approximately similar to middle Asia, but it is more than European countries.

Table 3: Association Between anemia indexes and other variables (n = 184)

Variable	Hb Mean (SD)	Hct Mean (SD)	Ferritin Mean (SD)
Gender			
male	11.2 (1.8)	34.4 (5.6)	565.7 (496.1)
Female	10.7 (1.4)	33.7 (4.3)	710.4 (684.8)
T-test P value	0.07	0.37	0.09
Hospitalization in two month ago			
Yes	10.2 (1.7)	32.1 (5.3)	820.2 (806.9)
No	11.1 (1.6)	34.5 (5.1)	593.6 (542.2)
T-test P value	0.006	0.02	0.08
Education			
Primary	10.9 (1.3)	34.1 (4.4)	685 (668.9)
Under diploma	10.4 (1.8)	31.9 (5.8)	583.2 (428.7)
Diploma	11.5 (1.7)	35.8 (5.3)	531.8 (457.4)
University	10.6 (1.9)	32.7 (5.4)	628.8 (587.7)
ANOVA			
F P value	3.51 0.01	4.07 0.008	0.75 0.5
Income			
Poor	10.9 (1.9)	33.6 (5.6)	833.6 (842.4)
middle	11.2 (1.4)	34.9 (4.6)	567.9 (468.2)
good	10.3 (2)	31.6 (6.1)	599.1 (632.2)
ANOVA			
F P value	3.48 0.03	5.1 0.007	2.9 0.06

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In comparison with Morgan study conducted in 1988 on hemodialysis patients that used Red cell distribution width (RDW) for iron deficiency screening and calculated RDW sensitivity (higher than 14.5) in to showing of decrease in iron stores [39], in this study was found no significant relation between red cell indices (RDW) and iron deficiency anemia. This finding may be due to the multi factorial characteristic of anemia in patients with chronic renal failure and or chronic inflammation resulted from the release of inflammation mediators in chronic renal failure. It seems that RDW is not a good criterion for estimating iron in hemodialysis patients and iron deficiency diagnosing and using from collection criteria example, serum iron, ferritin, red cell indices and RDW is necessary.

High blood pressure was most prevalent cause for chronic renal failure in the patients of this study, while in most of the European countries; diabetes is the most common cause for nephropathy. Maybe the reason is the differences in nutrition and lifestyle between Iran and other countries.

5. Conclusions

The functional iron deficiency was observed in about half of hemodialysis patients and could cause resistance and inappropriate response to Erythropoetin in them. Therefore nurse awareness and his/her duly action in determining the status of iron stores prior to the administration of erythropoietin prevents from prescribing an expensive drug and imposing unnecessary costs to the patient and the health care system.

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