Original Article

Classification of anemia in hemodialysis patients in relation to vascular access and its correlation with hepcidin and ferritin

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Abstract:

Background: Anemia is very common in patients with chronic kidney disease, and becoming almost universal in end stage renal disease, where dialysis or renal transplantation becoming the treatment of choice. High levels of hepcidin appear to accompany reduced renal function and serum ferritin may also be elevated.

Objectives: To classify anemia in hemodialysis patients and to display the correlations between the types of anemia and inflammatory parameters like hepcidin and ferritin according to vascular access of hemodialysis.

Patients and methods: This case-control study was conducted at Al-Hayat center for hemodialysis, and included 60 adult patients on hemodialysis. Also 20 healthy individuals were recruited as control group. Measurement of hemoglobin, erythrocyte sedimentation rate, transferrin saturation percentage, serum ferritin, C-reactive protein and hepcidin were done. Anemic patients were classified into; anemia of chronic disorder, iron deficiency anemia, combined, and others. Patients were also divided into two groups depending on their vascular access of hemodialysis.

Results: Anemia of chronic diseases was the most frequent anemia (45%) among the patients followed by combined anemia of chronic diseases/iron deficiency anemia then iron deficiency and other causes. No significant difference was observed between types of anemia and inflammatory parameters according to patients' vascular access of hemodialysis. There was no significant difference in the mean levels of hepcidin, ferritin, ESR and CRP of the patients according to the vascular access of hemodialysis, while hemoglobin level of patients with ACD in double lumen was significantly lower than those with arteriovenous fistula, P= 0.007.

Conclusions: Anemia of chronic diseases was the most frequent in HD patients. There are higher levels of inflammatory parameters in HD patients than healthy controls.

Key words: Hemodialysis, anemia, hepcidin, ferritin, CRP.

Introduction

Chronic kidney disease (CKD) is a kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for 3 months or more, irrespective to cause. Kidney damage in many kidney diseases can be ascertained by the presence of albuminuria(albumin tocreatinine ratio >30 mg/g in two of three spot urine specimens) [1].

Kidney disease severity is classified into 5 stages according to the level of GFR. Stages 3–5 may be defined by GFR alone, whereas stages 1 and 2 also require the presence of persistent proteinuria, albuminuria or hematuria, or structural abnormalities [2].

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End-stage renal disease (ESRD) corresponds to stage 5 CKD with GFR<15 ml/min/1.73m^2, all these patients are treated by dialysis or renal transplantation. The two forms of dialysis include peritoneal dialysis and hemodialysis [2].

Hemodialysis (HD) is the most common method used to treat advanced and permanent kidney failure. There are two types of vascular access in HD; double lumen (DL) and arteriovenous fistula (AVF) [3].

The Kidney Disease Improving Global Outcomes Anemia Work Group recommends that health care providers diagnose anemia in adult (older than age 15) males when their hemoglobin (Hb) falls below 13 g/dl and in females when it is less than 12 g/dl [4].

Anemia commonly occurs in people with CKD. It might begin to develop in the early stages, when someone has 20 to 50 percent of normal kidney function and tends to worsen as disease progresses [5]. It is caused by erythropoietin (EPO) deficiency, blood loss, iron deficiency, shortened red cell life span,

vitamin deficiencies, the "uremic milieu," and inflammation [2]. Inflammation is a rapid and acute protective response to infection or trauma. The activation of the complement pathway stimulates the degranulation of mast cells and the release of inflammatory cytokines [6].

Chronic inflammation plays an important role in the disease process and high levels of inflammatory markers appear to accompany reduced renal function [7].Within the pre-dialysis CKD population the prevalence of inflammation is great and is an important indicator of patient health and outcome butthe actual effect of chronic inflammation on renal function is unclear,and the relationship between the level of inflammation and GFR has not been found to correlate as may be expected [8,9].

Hepcidin, a 25-amino-acid peptide secreted by the liver, profoundly influences iron metabolism. It is the principal iron-regulatory hormone that mediates the homeostasis of extracellular iron concentrations [10,11].It inhibits iron absorption, placental iron transfer, and iron release from the reticuloendothelial system, and it mediates the anemia of inflammation [12].

Serum ferritin is an acute phase reactant and thus may be elevated in a number of conditions, including infections, inflammation, malignancy, and liver disease. Many of these conditions are common in CKD patients [13,14].

C-reactive protein (CRP) is also an acute phase protein and its production in the liver is adjusted by various cytokines, particularly interleukin 6 (IL–6). It should be noted that in the absence of inflammation, the plasma level of CRP is low; however, it can increase by 1000 times in reaction to inflammatory phenomena. The apparent increase in CRP level in HD patients indicates inflammation and is also known as a sensitive and independent marker for malnutrition. It is revealed that CRP is a powerful factor in predicting the complications and mortality in HD patients, especially in case of cardiovascular diseases [15,16].

Patients, materials and methods

This case-control study was conducted at Al-Hayat center for hemodialysis in Al-Karama hospital, Baghdad, Iraq from 1 November 2013 to 31 January 2014. The study population consisted of 60 adult patients (44 males and 16 females) with documented ESRD. They were on repeated HD sessions, 4 hours each (2-3 times per week) with different durations of illness (1-120 months). The following data were analyzed for all patients:

Age, gender,vascular access and duration of HD.

Hb level was measured by hemoanalyser(Human, Germany) and erythrocyte sedimentation rate (ESR), manual method.

Serum iron,total iron binding capacity, ferritin and C-reactive protein (CRP), all were measured by bioanalyser 300, (Human, Germany).

Serum hepcidin was measured by enzyme-linked immunosorbent assay (ELISA).

Anemia was considered when Hb level is < 13 g/dl in males and <12 g/dl in females [4]. Anemic patients were classified into groups according to the following criteria of Santen S et al. with modification [17]:

- Anemia of chronic disorder (ACD) if active inflammation (CRP≥6 mg/l and/or ESR ≥30 mm/1st hour) was present and 2 conditions were met, transferrin saturation percentage (TSAT%)≥20% and serum ferritin level ≥50 ng/ml;
- Iron deficiency anemia (IDA) if active inflammation was absent and 2 conditions were met, TSAT <20% and ferritin <200 ng/ml;
- Combined (ACD/IDA) if active inflammation was present and 2 conditions were met, TSAT <20% and ferritin level >200 ng/ml.

Patients were also divided into 2 groups depending on their vascular access of HD whether DLor AVF.

Twenty normal healthy individuals (age- and sex-matched) had been included as a control group in this study and were subjected to the same investigations of the patients.

Statisticalanalysis. Descriptive statistics were presented as mean, standard deviation, standard error of mean, and frequencies (%).Student's *t*-test, Fisher's exact test and Pearson's correlation werealso used.*P*value ≤0.05 indicated significant difference.

Results:

Age and gender. The mean age of the HD patients was 50.0 ± 16.2 years (range 15-74 years). The majority of patients (70%) aged >45 years. Male to female ratio was 2.8:1.

Hemodialysis. The vascular accesses of HD wereAVF in 61.7% patients and DL in 38.3% of them (Figure 1). The duration of patients being on HD varied from 1 month -10 years. The median frequency of dialysis was 3 times/week (range: 2-3 times/week).

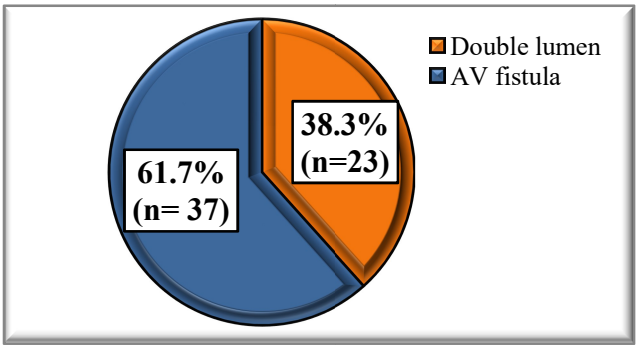

Figure 1. Vascular access of HD in 60 ESRD patients

Frequency and types of anemia in relation to vascular access of HD. Anemia was encountered in 95% (57/60) of ESRD patients and the remaining 3 patients (5%) were non-anemic. ACD alone was the most frequent (45%), IDA alone was found in only 7/60 patients (11.7%), while combined ACD/IDA was found in 15/60 patients (25%), and 13.3% (8/60) constituted the "other" causes of anemia. No significant difference was observed between anemic and non-anemic patients according to theirvascular access, *P*>0.05 (Table 1). All patients on DL HD were anemic and 8.1% of patients on AVF HD were non-anemic.

Table 1.Types of anemia classified according to the vascular access of HD of 60ESRD patients

Variable	Double lumen		AV fistula		Total no. of patients	Total %	
	No.	%	No.	%			
Anemic							
ACD	10	43.5	17	46.0	27	45	
IDA	2	8.7	5	13.5	7	11.7	
IDA/ACD	7	30.4	8	21.6	15	25	95
Others	4	17.4	4	10.8	8	13.3	
Non anemic	0	0.0	3	8.1	3		5
Total	23	100	37	100	60	100	

Fisher's exact test = 2.7, *P* = 0.62

Inflammatory parameters. Serum hepcidin was increased>15 ng/ml in 93.3% (56/60) of patients.Serum ferritin was increased ≥250 ng/ml in 31.7% (19/60) of patients. Serum CRP was increased ≥6 mg/ml in 56.7% (34/60) of patients. ESR was >30 mm/1st hour in 50% (30/60) of patients. The mean value of hepcidin, ferritin, CRP and ESR were all higher in patients group than in control group with statistically significant differences with *P* values<0.001, 0.002, 0.005 and <0.001, respectively (Table 2).

Table2. Comparison of inflammatory parameters of 60 HD patients and 20 controls

Parameter	Patients		Controls		*t*-test	*P*value
	Mean	SE	Mean	SE		
Hepcidin (ng/ml)	186.1	28.4	4.7	0.9	3.7	< 0.001
Ferritin (ng/ml)	280.8	35.1	83.6	14.5	3.2	0.002
CRP (mg/l)	8.6	1.1	3.0	0.2	2.9	0.005
ESR (mm/1sthr)	42.3	4.7	6.2	0.8	4.4	< 0.001

Anemia and inflammatory parameters. Hb had negative correlation with hepcidin, ferritin, CRP, and ESR, but none was found to be statistically significant (Table 3).CRP had a significant positive correlation with hepcidin (*P*= 0.001), ferritin (*P*= 0.029), and ESR (*P*= 0.003).Hepcidinshowed a significant positive direct correlation with ferritin,*P*= 0.003 (Figure 2).

Table 3.Pearson's correlation testmatrix forhepcidin, ferritin, CRP, and ESR/ Hb in 60 HD patients.

All patients		Hb	Hepcidin	Ferritin	CRP
Hepcidin	r	-0.035			
	P	0.791			
Ferritin	r	-0.047	0.381		
	P	0.720	0.003		
CRP	r	-0.079	0.402	0.283	
	P	0.549	0.001	0.029	
ESR	r	-0.214	-0.015	0.245	0.376
	P	0.100	0.910	0.059	0.003

r, correlation coefficient, ranged (0-1), the larger r value indicated the stronger correlation; minus sign, indicated inverse correlation.

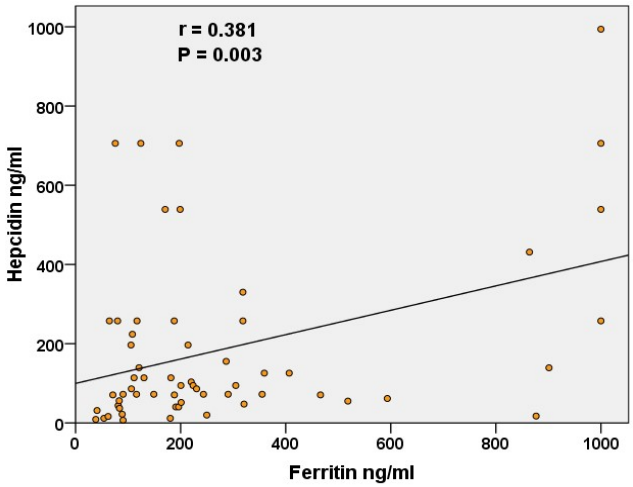

Figure 2. Direct (positive) correlation between hepcidin and ferritin of 60 ESRD patients

The effect of vascular access of HD on inflammatory parameters andHb level in types of anemia. In general, there were no significant differences in the mean levels of hepcidin, ferritin, ESR and CRP inHD patients according to theirvascular access though all of these parameters were higher in AVF than in DL patients(*P*>0.05), while there is significant difference regarding Hb level. Regarding the two types of anemia (IDA and ACD), the mean levels of serum hepcidin, serum ferritin and ESR for patients with AVF werehigher

than that of DLbut without significant statistical differences. IDA was associated with higher level of CRP but also was statistically insignificant (*P*=0.15). The meanHb level of HD patients with ACDinDL was lower than that in AVFshowing statistically significant difference,*P*=0.007 (Table 4).

Table 4. Comparison of inflammatory parameters between two types ofvascular access of HD according to their type of anemia

Parameter	Type of anemia	Vascular access of hemodialysis		*P* value
		Double lumen	AV fistula	
		Mean	Mean	
Hepcidin (ng/ml)	IDA	140.7	178.0	0.66
	ACD	179.2	211.6	0.69
	60 patients	164.1 ± 43.4	199.8 ± 37.5	0.55
Ferritin (ng/ml)	IDA	228.4	340.2	0.27
	ACD	257.4	281.9	0.80
	60 patients	246 ± 40.1	302.4 ± 51.3	0.44
CRP (mg/l)	IDA	11.9	5.8	0.15
	ACD	8.8	8.8	0.99
	60 patients	10 ± 2.4	7.8 ± 1.1	0.33
ESR (mm/1sthr)	IDA	33.1	36.9	0.80
	ACD	45.6	46.7	0.94
	60 patients	40.7 ± 7.7	43.2 ± 6.1	0.80
Hb (g/dl)	IDA	9.61	9.59	0.99
	ACD	8.88	10.57	0.007
	60 patients	9.16 ± 0.34	10.22 ± 0.32	0.034

Discussion

Persistent anemia is a common complication for patients with CKD [18],arising from declining erythropoietin production [19].The anemia management guidelines recommend treating and raising Hb levels to 10 - 12 g/dl and using the lowest possible erythropoietin stimulating agents' dosages to avoid the need for RBCs transfusions [20].This study included patients on acute and chronic HD and the duration ranged from one month to 10 years that leads to lower mean duration of HD in our study than that of Rasheed N et al.in Iraq[21]and Chen J et al. studyin USA [22].Anemia was reported in 95% of ESRD patients (Table 1). ACD alone was the most frequently encountered in HD patients followed by combined ACD/IDA, IDA alone was found in only 7 patients (11.7%), while 13.3% (8/60) constituted the "other" causes of anemia, and none of them showed reticulocytosis. Insignificant difference was observed between different types of anemia and non-anemic patients according to the choice of vascular access of HD (*P*= 0.62). But regarding anemia; all patients on DL HD were anemic while 8.1% of AVF patients werenon-anemic.In agreement with Rasheed N et al. study[21],the present study demonstrated that serum hepcidin and ferritin levels were significantly higher in HD patients than in control subjects as illustrated in Table 2 (*P*<0.001 and 0.002, respectively) and showing direct (positive) correlation between them (Figure 2, *P*= 0.003).This is consistent with results of Urrehaga E et al. studyin Spain [23] and Eleftheriadis T et al. studyin Greece [24].Raised serum hepcidin level appears to be multifactorial, hepcidin production is regulated by iron, inflammation and erythropoiesis [25,26]. Hepcidin inhibits iron flows into plasma from macrophages involved in recycling of senescent erythrocytes, duodenal enterocytes engaged in the absorption of dietary iron, and hepatocytes that store iron [27]. It is increased in patients with severe inflammatory diseases or chronic infections [28].Anemia is the predominant hepcidin expression regulator, since anemia suppresses hepcidin even in the presence of iron overload [29].CRP was evident among HD patients showing statistically significant difference when compared with control group (*P*= 0.005). CRP is significantly related through shared risk factors to CKD with GFR < 60 ml/min/1.73m^2 [30],as hypertension, diabetes and obesity are strongly related to systemic inflammation and renal dysfunction [3,31].Serologically, an activated inflammatory response was found in 30% - 50% of ESRD patients [32],which might be ascribed to the terminal renal disease and/or the dialysis procedure itself [33].Uremia-related causes include accumulation of advanced glycation end-products, production of reactive oxygen species leading to oxidative damage, and reduced renal clearance of proinflammatory cytokines and acute phase reactants [34].The present study also revealed a significant association between high ESR level and ERSD patients. ESR is elevated (greater than 25 mm/1st hour by the Westergren method) in almost all patients with the nephritic syndrome or ESRD [35].All inflammatory parameters showed statistically insignificant inverse correlation with anemia,but it seems that CRP and ESR are more related to anemia (larger r- value) when compared with hepcidin and ferritin.Some patients with CKD show dysregulation of iron metabolism and develop ACD [36]. A hallmark of ACD is abnormal iron homeostasis associated with increased uptake and retention of iron by cells in the reticuloendothelial system (RES). This might lead to diversion of iron from the circulation to storage sites within the RES that limits the availability of iron for erythroid progenitor cells, and iron-restricted erythropoiesis [37].Anemia was more evident in patients with DL than with AVF showing statistically significant difference (*P*= 0.034), and were significantly associated with lower level of Hb particularly in patients with ACD (*P*= 0.007). This suggests that AVF

is better associated with higher level of Hb. This reduction in Hb level was noticed to be associated with higher level of CRP than seen in patients with AVF but this association was statistically insignificant(*P*= 0.33). Also there was no statistically significant correlation between levels of hepcidin, ferritin, ESR and CRP with different types of anemia. These findingsare similar to results of Pisoni R, et al.study in USA [38]. The insignificant higher levels of hepcidin, ferritin and ESR in AVF patients did not show to exert a higher impact on the severity of anemia compared with DL patients. These findings are inconsistent with results of Saxena AK et al. studyin Saudi Arabia [39].

Conclusion:

The frequency of ACD was the highest among anemia in HD patients followed by ACD/IDA.HD patients had higher levels of inflammatory parameters than healthy controls but these do not significantly varybetween DL and AVF. Anemia is more in patients with DL than those with AVF.

Author Contributions:

All authors confirmed they have contributed to the intellectual content of this paper and have met the following requirements:

(a) Significant contributions to the conception and design, data analysis and interpretation;

(b) Drafting or revising the article for intellectual content; and

(c) Final approval of the published article.

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