Original research

Description of iron deficiency in patients with end-stage chronic kidney disease on hemodialysis, Quito, Ecuador

Descripción de la ferropenia en pacientes con enfermedad renal crónica terminal en hemodiálisis, Quito, Ecuador

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Abstract

Introduction: Anemia and iron deficiency are very prevalent conditions in hemodialysis and have been associated with an increase in morbidity and mortality.

Objective: Describe the characteristics of iron deficiency and anemia in patients with end-stage renal disease on hemodialysis, and analyze the parameters of the blood count to predict iron deficiency in them.

Materials and methods: A cross-sectional descriptive study carried out in the hemodialysis unit of the Specialties Hospital of the Armed Forces No. 1 and CLINEF Norte, Quito, Ecuador, during December 2018 and January 2019. The analysis was based on the comparison of two groups, ferropenic and non-ferropenic patients.

Results: We included 268 patients with an average age of 59.16 years; 89 patients (33.21%) were ferropenic. However, they presented normal hematimetric parameters in most of them. We also found that 80.22% of the patients included were anemic, with little frequency of microcytosis and hypochromia. Among them, 33.21% were ferropenic, being hemoglobin a poor marker of iron deficiency. Additionally, to predict ferropenia, and not to have ferritin or transferrin saturation, we find especially useful the mean corpuscular hemoglobin, mean corpuscular volume, erythrocyte distribution width, and Srivastava index, however the predictive value increases when including the syderemia as in our proposed model.

Conclusions: Given the high frequency of anemia without hypochromia or microcytosis in patients with end-stage renal disease on hemodialysis, even in iron deficiency, regular evaluation of ferric metabolism is essential, as well as the analysis of the blood count with a focus on the dialysis patient.

Key words: Ferropenia, anemia, chronic kidney disease, hemodialysis.

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Resumen

Introducción: la anemia y ferropenia son condiciones muy prevalentes en hemodiálisis asociadas al incremento en la morbimortalidad.

Objetivo: describir las características de la ferropenia y anemia de pacientes con enfermedad renal terminal en hemodiálisis, y analizar los parámetros del hemograma para predecir la deficiencia de hierro en ellos.

Materiales y métodos: estudio descriptivo transversal realizado en la unidad de hemodiálisis del Hospital de Especialidades de las Fuerzas Armadas N°1 y CLINEF Norte, Quito, Ecuador, durante diciembre de 2018 y enero de 2019. El análisis se basó en la comparación de dos grupos, pacientes ferropénicos y no ferropénicos.

Resultados: se incluyeron 268 pacientes con edad promedio de 59,16 años; 89 pacientes (33,21 %) fueron ferropénicos, sin embargo presentaron parámetros hematimétricos normales en la mayoría de ellos. Encontramos además que el 80,22 % de los pacientes incluidos eran anémicos, con poca frecuencia de microcitosis e hipocromía. Entre ellos, el 33,21 % fueron ferropénicos, siendo la hemoglobina un pobre marcador de ferropenia. Adicionalmente, para predecir ferropenia, y de no contar con ferritina o saturación de transferrina, encontramos útil la hemoglobina corpuscular media, el volumen corpuscular medio, el ancho de distribución eritrocitaria y el índice de Srivastava, sin embargo el valor predictivo se incrementó al incluir la sideremia como en nuestro modelo propuesto.

Conclusiones: dada la alta frecuencia de anemia sin hipocromía o microcitosis en los pacientes con enfermedad renal terminal en hemodiálisis, incluso en ferropenia, es fundamental la evaluación regular del metabolismo férrico, así como el análisis del hemograma con enfoque en el paciente dialítico.

Palabras clave: ferropenia, anemia, enfermedad renal crónica, hemodiálisis.

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Introduction

Iron deficiency and anemia are frequent complications in patients with chronic renal failure (CRF), especially in those who require renal replacement therapy, being in this group a multifactorial pathology, with etiopathogenic elements such as relative erythropoietin (EPO) deficiency, uremia-induced inhibition of erythropoiesis, reduction in erythrocyte survival, as well as an alteration in iron homeostasis.[1] In addition, anemia has been associated with an increase in mortality, as well as with a reduction in the quality of life of patients with CKD,[2] however, the excessive increase in hemoglobin (Hb) as well as the iron overload during the use of erythropoiesis stimulating agents (ESA) have also been associated with complications due to iron toxicity.[3] This is why the management of anemia and iron deficiency in CKD have been restricted until establishing a hemoglobin value, whose excess or deficiency would be prevented.[4]

Although transferrin saturation and ferritin determination are useful tests to determine a state of iron deficiency, there are centers that do not have frequent access to such tests. Therefore, the objective of this study is to describe the characteristics of iron deficiency and anemia, and to analyze the parameters of the blood count, alone or through established indices to predict the status of iron deficiency in patients with CKD treated in the hemodialysis unit of the Specialties Hospital of the Armed Forces No. 1 (HE-1) and in the hemodialysis clinic CLINEF Norte, both institutions located in Quito, Ecuador.

Methodology

This is a study of cross-sectional descriptive design conducted in the hemodialysis unit of the HE1 and CLINEF Norte, Quito, Ecuador, during the months of December 2018 and January 2019, which included by convenience sampling 268 patients diagnosed with chronic kidney disease under renal replacement therapy such as hemodialysis. In this group of patients, according to the routine evaluation protocol, the study of hematological parameters, as well as of iron metabolism were performed, both using automated analyzers.

The blood count included values such as mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red blood cell distribution width (RDW), red blood cell count (RBC), hematocrit (Hct), hemoglobin (HB). The normality ranges used were MCV 80-100 fl, MCH 26-34 pg, and RDW up to 14.5 %.

The hematological parameters were determined through a Mindray BC6800 automatic analyzer, which performs a 3D analysis using the information obtained by the laser light scattering, as well as fluorescence signals, at the passage of each cell. Additionally, it uses a colorimetric method to measure the hemoglobin.

Indices for assessment of iron deficiency

Looking for a way to predict iron deficiency anemia, we employed commonly used indices to differentiate iron deficiency anemia from thalassemia such as: Mentzer (MCV/RBC), RDWI (RDW* MCV/RBC), and Srivastava (MCH/RBC)

Definition of anemia, target hemoglobin, and iron deficiency

The WHO defines anemia as an hemoglobin value lower than 13 g/dl in men and lower than 12 g/dl in women,[5] however, it has been recommended to use a hemoglobin range called “target” between 10 and 11.5 g/dl.[4] In addition, we use as a definition of iron deficiency a ferritin level < 100 ng/ml or a transferrin saturation lower than 20%.[4,6]

Statistical analysis

The data were tabulated and analyzed using the SPSS and Excel software, both in their latest versions for Windows 10. We classified all patients into two groups, patients with ferropenic status, and patients without ferropenia. In these groups we conducted a

difference in means between all the determined hematimetric parameters, and then we used the linear discriminant analysis to determine the variables with the greatest effect to predict iron deficiency, as well as to generate a new predictive model. To establish the cut-off points in the evaluation of hematimetric parameters and indices, we used the data provided by the ROC (Receiver Operating Characteristic) curves. Finally, each parameter was studied as a diagnostic test by sensitivity, specificity, positive and negative predictive values, accuracy index, and diagnostic OR (DOR).

Results

Among the 268 patients included, there were a greater number of men, 146 (54.48%). Likewise, when considering the time during which our patients have remained on hemodialysis we found that 2.99 % have remained for more than 10 years, 24.25 % between 5 and 10 years, 21.64 % between 3 and 5 years, 34.33 % between 1 and 3 years and 16.79 % less than one year.

Regarding the age groups, 54.10% of our patients were in the group between 60 and 94 years, being the most affected age group, in contrast, the least affected group (6.72%) was that of people between 21 and 30 years of age. The average age was 59.16 years, with a maximum and minimum age of 94 and 21 years.

According to the state of iron deficiency, 89 patients (33.21%) were ferropenic, while 179 (66.79%) were non-ferropenic.

Anemia by definition of the WHO

Using the definition of the WHO we identified that 215 patients (80.22 %) presented anemia, of them, 3 individuals had microcytosis MCV < 80fl), and 6 had hypochromia (MCH < 26 pg). Regarding the degree of anemia, 6 (2.24%) were classified as severe anemia (HB <8 g/dl), 78 (29.10%) as moderate anemia, and 131 had mild anemia.

When dividing into groups, we found 64 (71.91%) anemic patients in the group of ferropenic patients, and 151 (84.36%) anemic patients in the non-ferropenic group.

Target hemoglobin

According to the definition of target HB, 93 (34.70%) of our patients were within this category. Among the group of those who did not reach a target HB, 49 exceeded the value of 13 g/dl; while 36 had HB less than 10 g/dl. However, it should be noted that 187 patients (69.78%) had the hemoglobin in a range between 10 and 13 g/dl.

Ferritin and transferrin saturation

A state of iron deficiency was found in 89 patients (33.21%). In contrast, 30 patients (11.19%) had a ferritin level higher than 1000 ng/ml. Among the ferropenic patients we could observe normal blood count values in 91.01%, 94.38%, and 42.67%, for MCH, MCV and HB, respectively. We found that 89.89% of ferropenic patients had a Srivastava index lower than 8.9, and in the same way, 89.89% of this group had a Mentzer index lower than 28.24, no patient had values indicative of thalassemia. A RDWI index lower than 365 as indicative of iron deficiency was found in 65.17% of ferropenic patients, being the least frequent among the three indices used.

Difference in means

When comparing the average of the values obtained between the two groups, we found statistically significant differences for all the parameters studied, except in the HB values. Table 1 summarizes these findings.

Note. RDW, red blood cell distribution width; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin, MCV, mean corpuscular volume; HCT, hematocrit; RBC, number of red blood cells; RDWI; Red cell distribution width index; HB, hemoglobin.

Proposed models

When performing the linear discriminant analysis, we found that the most influential variables to predict

Table 1. General characteristics of the patients included.

Total	N	%
	268	100
Gender		
Men	146	54,48
Women	122	45,52
Age (years)		
60 to 94	145	54,10
30 to 60	105	39,18
21 to 30	18	6,72
Time on hemodialysis (years)		
<1	45	16,79
1 to 3	92	34,33
3 to 5	58	21,64
5 to 10	65	24,25
10	8	2,99
Iron deficiency	89	33,21
Non-iron deficiency	179	66,79

iron deficiency were MCH, MCV, and the Srivastava index, so starting from these variables we generated a first predictive model consisting of the equation; 0.966*MCH + 0.824*MCV + 0.766* Srivastava (model 1). In addition, we carried out another model including the determination of serum iron, which is given by the equation; 0.784*MCH + 0.731*MCV + 0.669* Srivastava + 0.622*Iron.

ROC curves

The obtention of the cut-off points to estimate a state of iron deficiency through the included parameters was carried out using ROC curves. Table 2 presents the value of the area under the curve for each parameter.

Along with this, the sensitivity and specificity for each parameter was established, with the cut-off points with better sensitivity compared to the conventionally used cut-off points. These results are shown in Table 3.

Table 2. Means and differences in means of the findings of the blood count.

Parameters	Mean in ferropenic patients	Mean in non-ferropenic patients	Difference in means	95% CI	p-value
RDW	15,92	14,81	-1,10	-1,5647 a -0,6353	< 0,01
MCHC	32,36	32,90	0,54	0,2761 a 0.8039	< 0,01
MCH	29,01	31,05	2,04	1,4955 a 2.5845	< 0,01
MCV	89,62	94,37	4,75	3,2664 a 6.2336	< 0,01
HCT	36,49	34,82	-1,67	-2,9631 a -0,3769	0,01
RBC	4,10	3,70	-0,40	-0,5658 a -0,2342	< 0,01
Srivastava	7,36	8,63	1,27	0,8424 a 1,6976	< 0,01
Mentzer	22,75	26,22	3,47	2,1597 a 4,7803	< 0,01
RDWI	357,31	388,30	30,99	8,8109 a 53,1691	< 0,01
HB	11,81	11,44	-0,37	-0,7925 a 0,0525	0,09

Note: RDW, red cell distribution width; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin, MCV, mean corpuscular volume; HCT, hematocrit; RBC, number of red blood cells; RDWI; Red cell distribution width index; HB, hemoglobin.

Table 3. Area under the curve found for ROC curves.

	AUC	95 % CL		P value
		Lower limit	Upper limit	
RDW	0,64	0,58	0,71	<0,01
MCHC	0,63	0,56	0,7	<0,01
Mentzer	0,7	0,63	0,77	<0,01
MCV	0,71	0,65	0,78	<0,01
Srivastava	0,722	0,66	0,79	<0,01
Model 1	0,73	0,67	0,79	<0,01
MCH	0,75	0,69	0,81	<0,01
Serum iron	0,79	0,73	0,85	<0,01
Model 2	0,81	0,75	0,87	<0,01

Note. AUC, area under the curve; ROC, receiver operating characteristic curve; RDW, red cell distribution width; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin.

Discussion

Patients with end-stage CKD with renal replacement therapy such as hemodialysis have anemia as a common comorbidity, being in this population a pathology whose etiology can be multifactorial or due to multiple deficiencies.[7] Among these factors we can point out the importance of the relative deficiency of EPO and also the resistance to ESA, which would make it difficult to overcome anemia under the conventional definition established by the WHO, with the risk of adverse effects such as sustained hypertension, cardiovascular events , or thrombotic events that could even affect vascular accesses.[8,9] In our findings we identified a high percentage of anemic patients according to the definition of the WHO, but in contrast we had a high percentage of patients that met an acceptable value of HB,[10] (10-13g/dl) in the same way, and regarding the consideration of multifactorial anemia in hemodialysis, there was no significant difference between the hemoglobin of ferropenic and non-ferropenic patients. These results are similar to those presented in other studies with a prevalence of anemia in hemodialysis close to 80%.[11] In addition, the state of chronic inflammation in patients with CKD and on HD, has been associated with an increase in hepcidin, an acute phase protein which has been described as a limiting molecule in the bioavailability of iron in CKD, a fact that added to its renal excretion, would hinder iron supplementation in these patients.[12] It has been reported that hepcidin levels are higher in hemodialysis patients compared with healthy controls (424 ± 174.2 ng/mL vs. 72.4 ± 12.3 ng/mL; p <0.01), in addition, it was found a negative correlation between hepcidin levels and reticulocyte count (r = -0.63, p = 0.015).[13] The effects of these pathophysiological phenomena could be present in our population, in whom we have been able to evidence iron deficiency despite complying with ferrous supplementation protocols

Although characteristics such as hypochromia and microcytosis have been described as typical of iron deficiency, a small group of our ferropenic patients presented these conditions, which leads us to analyze this clinical condition in a more complex way than that which has been classically proposed.[14,15] In this context it is also important to mention another factor in these patients, and it is the one associated with vitamin B12 deficiency, which pathophysiologically presents with macrocytosis and could hide the typical microcytosis of iron deficiency, which could explain why most of our ferropenic patients have hematimetric parameters within normal ranges.[16,17] This difficulty in interpreting the tests was evidenced in our results when we saw how at different cut-off points the predictive power changed, especially considering that the majority of ferropenic patients had anemia with normal values in MCV and MCH, however, being close to the classically used intervals, we consider the RDW as a parameter that should always be evaluated. In this context, we consider as tools less complicated in their interpretation the use of indices for our population as the Srivastava index, with a cut-off point of less than 8.9 as defining iron deficiency, being a useful diagnostic tool, especially when the values of ferritin or transferrin saturation are not available, however, it is important to keep in mind that a value lower than 3.8 suggests a beta thalassemia trait. These findings are novel because we identified new ways to use diagnostic tools, in this case to define iron deficiency.

Table 4. Evaluation of the parameters studied as diagnostic tests for iron deficiency.

	s	e	ppv	npv	ar	DOR
RDW ≥13.9 %	91,01	26,82	38,21	85,71	48,13	3,71
MCHC <33.7	89,89	18,99	35,56	79,07	42,54	2,08
MCH <31.8 pg	89,89	35,75	41,03	87,67	53,73	4,95
MCV <94.8 fl	89,89	25,14	37,38	83,33	46,64	2,99
HCT <35%	39,33	31,28	22,15	50,91	33,96	0,30
SRIVASTAVA <8.9	89,89	38,55	42,11	88,46	55,60	5,58
Mentzer <28.24	89,89	25,14	37,38	83,33	46,64	2,99
MODEL 1 <114.7	89,89	26,26	37,74	83,93	47,39	3,16
MODEL 2 <124	73,03	79,89	64,36	85,63	77,61	10,76
RDW ≥14.5 %	77,53	45,25	41,32	80,20	55,97	2,85
MCH <26 pg	8,99	99,4	88,9	68,7	69,4	17,6
MCV < 80 fl	5,62	98,88	71,43	67,82	67,91	5,27

Note. s, sensitivity; e, specificity; ppv, positive predictive value; npv, negative predictive value; ar, accuracy ratio; DOR, diagnostic OR; RDW, red cell distribution width; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin, MCV, mean corpuscular volume; HCT, hematocrit; RBC, number of red blood cells; RDWI; Red cell distribution width index.

In the same way, we could recommend the use of our proposed models, especially model 2, when the serum iron value is available.

Conclusions

Determining the probability that a patient is ferropenic is important in clinical practice because it allows us to start an iron trial before determining transferrin and ferritin saturation, which could be beneficial for not delaying iron supplementation when it is necessary.

Ferropenia and iron deficiency anemia are frequent conditions in patients with CKD on HD, however their differentiation with non-ferropenic anemic patients can be difficult, especially because several hematimetric parameters may be within normal ranges, even if a state of iron deficiency coexists. For this reason, we recommend to include the analysis of new cut-off points for MCV, MCH, RDW, as well as the use of indices, especially Srivastava index. In addition, we propose two models for the study of iron deficiency, the first one without having serum iron defined by the equation 0.966*MCH + 0.824*MCV + 0.766* Srivastava, and the second including the determination of serum iron, given by the equation 0.784*MCH + 0.731*MCV + 0.669*Srivastava + 0.622*Iron. We consider important the need to assess new indices, as well as the correct interpretation of the hematimetric parameters, since CKD with the need for HD is a clinical condition with several peculiarities, one of them being iron deficiency, in which it is possible that the analysis of the diagnostic tests in a traditional way does not correspond to the reality of our patients, so it is important to study and validate the currently available diagnostic tools.

Conflict of interest

The authors do not have any conflict of interest to declare.

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Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

The authors declare that they have followed the protocols of their workplace on the publication of patient data.

Right to privacy and informed consent

The authors declare that patient data do not appear in this article.

Contribution of the authors

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