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Research Article

Factors Related to the Presence of Anemia in Patients with Chronic Kidney Disease in Hemodialysis

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Abstract

Introduction: The prevalence of anemia in Chronic Kidney Disease (CKD) is high. However, little is known about the factors related to anemia in patients with chronic Hemodialysis (HD) in Mexico.

Material and Methods: A cross-sectional study was conducted in adult patients with CKD undergoing HD in the northern area of Mexico City treated at the Mexican Institute of Social Security. Hemoglobin (Hb) and Hematocrit (Htc) levels, as well as clinical and biochemical factors associated with anemia, were evaluated.

Results: Data was collected from 747 patients, obtaining a mean hemoglobin of 9.7 g/dl (IQR 8.4-10.9 g/dl). The group was divided into two using Hb <10.0 g/dl and >10.0 g/dl as cutoff limits. Fifty six percent of the patients had hemoglobin ≤10.0 g/dl. Hb level <10.0 g/dl were associated with DM (OR 1.49, IC 95% 1.06-2.10, p=0.001), hyperphosphatemia (OR 1.69, IC 95% 1.21-2.28, p=0.001), high calcium-phosphate product (OR 1.43, IC 95% 1.01-2.03, p=0.040) and iron deficiency (OR 1.95, IC 95% 1.38-2.75, p=0.001). Glomerulopathies (OR 0.44, IC 95% 0.22-0.90, p=0.026), female gender (OR 0.55, IC 95% 0.40-0.074, p=0.001) and erythropoietin administration (OR 0.57, IC 95% 0.39-0.82, p=0.002) were associated with hemoglobin ≥10 g/dl.

Conclusion: The factors associated with Hb <10.0 g/dl were mineral-bone metabolism disorders and iron deficiency. The periodic evaluation of quality-of-care indicators of HD treatment, such anemia, are necessary to detect improvement opportunities.

Keywords: Anemia; Hemodialysis; Associated factors

Background

Anemia is one of the earliest and most frequent manifestations of Chronic Kidney Disease (CKD).

CKD anemia is of multifactorial origin [1,2]. However, the immediate cause is the inadequate production of endogenous Erythropoietin (EPO) due to atrophy or injury to the renal peritubular cells responsible for its synthesis that, consequently, decreases the production of erythrocytes, promotes the apoptosis of erythroid progenitors and lessens the proliferation and differentiation of proerythroblasts and normoblasts [3]. Iron is another important factor related to the development of anemia; iron deficiency in CKD is frequent and reduces the synthesis of hemoglobin. Iron deficiency is a consequence of insufficient intestinal absorption associated to a chronic inflammatory state. On the other hand, gastrointestinal losses and during Hemodialysis (HD) can contribute significantly [4].

The factors involved in CKD anemia include hyperparathyroidism, a complication secondary to phosphorus retention that decreases the response to EPO [3-6]. The deficiency of folates or vitamin B12 also contributes to the development of anemia, specifically the macrocytic type, which has a frequency of 5% approximately, a proportion that may be higher in patients in HD, suggesting loss of vitamin B12 and folic acid during the HD [7].

The Angiotensin-Converting Enzyme Inhibitors (ACEI) and the Angiotensin Receptor Blockers (ARB) often employed in patients with CKD, participate in the production of anemia by inhibiting the erythropoietic effects of angiotensin II, in addition to reducing the EPO synthesis by increasing the renal blood flow [8-10].

In CKD, anemia is an independent risk factor to myocardial injury, it favours the development and progression of left ventricle hypertrophy and heart failure [11,12], additionally, increases the number of hospitalizations contributing to a declining quality of life and higher mortality [1,13]. Previous studies have shown that hemoglobin levels <8 g/dl and hematocrit <30% are associated with twice the risk of death compared to patients with hemoglobin between 10-11 g/dl and hematocrit among 33-36%. [14,15].

On account of its high frequency, its impact on the patients' quality of life, and mainly because it is susceptible to intervention, the control of anemia is considered a quality-of-care indicator and has been included in international studies such as Dialysis Outcomes and Prescription Patterns Study (DOPPS) as an evaluation criteria, establishing the reference values that are associated with the best clinical outcome. Only developed countries participate in these studies, nevertheless its extension to developing countries is also highly important.

In Mexico's case, the utmost proportion of patients in HD are

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treated by a single social security institution, IMSS. This institution outsources HD to private organizations through specific contracts in which certain management criteria are established, including anemia control. However, regarding the patient management both HD providers and IMSS participate, the latter with specialized consultations and input supply (EPO, supplemental iron, hematology consultation and drugs related). The coordination of this joint responsibility is complex, therefore the information related to the control of anemia is insufficient.

Based on the forementioned, the goal of this study was to identify the frequency in which the optimal levels of hemoglobin and hematocrit are achieved and the factors associated to the presence of values lower than those recommended in a population of patients receiving subrogate HD (extramural) by the Mexican Institute of Social Security (IMSS).

Materials and Methods

Design: A cross-sectional study was conducted with the total current patients treated in HD units outsourced by IMSS in the northern metropolitan area of Mexico City by December 31, 2019.

Patients: We included adult patients with CKD diagnosis from any cause, with no upper age limit, of either gender, treated in subrogated HD units. We excluded patients with less than three HD sessions per week and patients with chronic or acute infectious diseases documented at the beginning of the HD program. Pregnant patients and patients with bleeding history within 3 months previous to the study, were also excluded. Patients who deceased or had bleeding episodes during the study period were eliminated.

Data collection: The last serum hemoglobin value documented at the HD unit from every patient by December 31, 2019 was registered. Patients were classified into two groups according to the levels of hemoglobin establishing as cutoff values less than 10 g/dl (regarding the fulfilment of Hb goals in CKD patients) and patients without anemia for those with hemoglobin level >10 g/dl. Mean corpuscular volume, serum iron, transferrin saturation percentage and ferritin were recorded for both groups, as well as PTH concentration, number of transfusions, treatment with ACEI o ARB, iron and EPO doses registered on the IMSS medical record.

Statistics: Data is presented as mean and standard deviation (and interquartile range) or as frequency according with the variable type and their distribution. Comparisons between groups were established with chi square and Student's t-test for variables with normal distribution, and Mann-Whitney U for those of free distribution. Variables with differences between groups were, subsequently, included in the logistic regression multivariate analysis to identify risk factors for the presence of hemoglobin and hematocrit values <10 g/dL y 33%, respectively. The value of p-0.05 was considered significant. The statistical package SPSS version 25 was employed.

Results

Study population characteristics. Nine hundred and five patients were eligible, of them, 110 patients fulfilled the exclusion criteria and 48 were eliminated, therefore 747 patients were considered for the analysis. The demographic and clinical data of the 747 patients are shown on (Table 1). The most frequent etiology for CKD was diabetes mellitus (24.9% of patients) and arterial hypertension (16.3%). Primary glomerulopathies were the cause in 5.5% of patients and less than 5% were found to originate secondarily from other entities, such as preeclampsia, polycystic kidney disease and vesicoureteral

Table 1: Baseline characteristics.

Variable	*Mean*	*(±) SD*	*Median*	*IQR 25-75*
Age (years)	50.61	15.64	51	37-63
Weight (kilograms)	66.36	15.24	65	56-75.5
Height (meters)	1.61	0.09	1.6	1.54-1.69
BMI (kg/m^2)	25.47	4.97	24.57	22.05-28.22
Hemoglobin (g/dL)	9.7	1.83	9.7	8.4-10.9
MCV (fl)	92.29	8.19	92.8	87.97-97.90
Calcium (mg/dL)	8.37	1.13	8.4	7.7-9.0
Phosphorus (mg/dL)	5.16	2.03	4.9	3.7-6.32
Calcium-phosphate product	43.16	18.05	40.5	30.10-53.63
Parathyroid hormone (pg/dL)	643.57	668.9	467	121.5-922
Serum iron (ug/dL)	59.9	38.43	51	35-72
Transferrin saturation (%)	25.29	21.04	19.96	12.24-30.61
TIBC (mcg/dL)	268.91	78.24	264.41	210.03-326.29
Transferrin (mg/dL)	215.27	62.42	211.5	211.5-261
Ferritin (ng/dL)	327.81	640.03	86	30-330.5
IV iron dose (mg/week)	238.7	304.32	100	100-300
EPO dose (UI/week)	10097	4240.11	12000	8000-12000
Number of transfusions	1.82	0.99	2	1-2

SD: Standard Deviation; IQR: Interquartile Range; BMI: Body Mass Index; MCV: Mean Corpuscular Volume; TIBC: Total Iron-Binding Capacity; IV: Intravenous; EPO: Erythropoietin.

Table 2: Mean differences by group of study.

Variable (Mean and SD ±)	*Patients with Hb <10 g/dL*	*Patients with Hb ≥10 g/dL*	*p*
Age (years)	48.55 (15.37)	52.27 (15.52)	**0.001**
Weight (kilograms)	65.97 (15.74)	67.18 (14.74)	0.297
Height (meters)	1.60 (0.10)	1.61 (0.09)	0.227
BMI (kg/m^2)	25.42 (5.19)	25.66 (4.73)	0.533
Hemoglobin (g/dl)	8.41 (1.08)	11.34 (1.15)	**0.001**
MCV (fl)	91.34 (8.44)	93.49 (7.71)	**0.001**
Calcium (mg/dl)	8.31 (1.14)	8.44 (1.11)	0.12
Phosphorus (mg/dl)	5.45 (2.07)	4.93 (1.98)	**0.001**
Calcium-phosphate product	45.92 (18.35)	40.99 (17.53)	**0.001**
Parathyroid hormone (pg/dl)	649.22 (759.49)	636.19 (557.13)	0.902
Serum iron (ug/dl)	56.22 (39.53)	64.58 (36.51)	**0.004**
Transferrin saturation (%)	24.62 (22.43)	26.16 (19.13)	0.331
TIBC (mcg/dl)	265.44 (84.04)	273.33 (70.06)	0.18
Transferrin (mg/dl)	212.71 (66.94)	218.53 (56.09)	0.215
Ferritin (ng/dl)	358.44 (589.44)	288.85 (698.14)	0.148
IV iron dose (mg/week)	268.88 (321.90)	217.77 (295.64)	0.435
EPO dose (UI/week)	10656.62 (4337.30)	9421.73 (4101.28)	**0.001**
Number of transfusions	1.83 (0.82)	1.78 (1.10)	0.779

Table 3: Bivariate analysis, anemia in HD patients. (n=747).

Variable	*OR*	*CI 95%*	*p*
Male gender	1.81	1.34-2.45	**0.001**
Female gender	0.55	0.40-0.74	**0.001**
Diabetes mellitus	1.49	1.06-2-10	**0.022**
Arterial hypertension	0.98	0.66-1.46	0.94
Glomerulopathies	0.44	0.22-0.90	**0.026**
High mean corpuscular volume	1.33	0.88-1.99	0.165
Hypocalcemia (<8 mg/dl)	0.77	0.56-1.05	0.109
Hypercalcemia (>10 mg/dl)	1.54	0.78-3.05	0.212
Hypophosphatemia (<2.5 mg/dl)	0.44	0.23-0.83	**0.012**
Hyperphosphatemia (>4.5 mg/dl)	1.69	1.21-2.28	**0.001**
Calcium-phosphate product (>55 mg^2/dl^2)	1.43	1.01-2.03	**0.04**
Hyperparathyroidism (PTH >300 pg/dl)	1.59	0.81-3.01	0.153
Iron deficiency (transferrin saturation <20%, ferritin <500 ng/dl)	1.95	1.38-2.75	**0.001**
Absolute iron deficiency (transferrin saturation <20%, ferritin <200 ng/dl)	1.96	1.41-2.72	**0.001**
Functional iron deficiency (transferrin saturation <20%, ferritin 200 a 500 ng/dl)	0.72	0.34-1.55	0.41
Iron overload (transferrin saturation >45%, ferritin >1000 ng/dl)	1.06	0.65-1.71	0.807
Transferrin saturation <20%	0.74	0.55-1.001	0.051
Transferrin saturation >45%	1.06	0.65-1.71	0.807
Serum TIBC <230 mcg/dl	0.70	0.51-0.97	**0.032**
Serum TIBC >380 mcg/dl	0.58	0.25-1.38	0.223
Serum transferrin <170 mg/dl	0.65	0.46-0.92	**0.015**
Serum transferrin >380 mg/dl	1.27	0.17-9.09	0.809
Serum ferritin <200 ng/dl	1.96	1.41-2.72	**0.001**
Serum ferritin >500 ng/dl	0.53	0.35-0.79	**0.002**
ACEI intake	0.54	0.27-1.10	0.091
ARB intake	1.03	0.76-1.39	0.84
B-complex vitamin intake	1.06	0.76-1.48	0.696
Folic acid intake	1.10	0.78-1.54	0.572
Oral iron intake	1.11	0.82-1.50	0.471
IV iron administration	1.31	0.84-2.05	0.222
EPO administration	0.57	0.39-0.82	**0.002**
Transfusion history	0.73	0.50-1.07	0.113

reflux, while forty-eight percent of patients did not have a determined etiology.

Consistent with the WHO definition of anemia and the KDIGO guidelines (<13 g/dl in men and <12 g/dl in women), 94.2% of the patients had anemia (n=676). For the purpose of this study, anemia was defined as Hb <10 g/dl, which was found in 56% of the patients (n=402). The mean level of hemoglobin was 9.7 g/dl, with a median of 9.7 g/dl (IQR 8.4 - 10.9 g/dl). The mean corpuscular volume mean was 92.29 ± 8.19 fl, median of 92.8 fl (IQR 87.97 - 97.90 fl) (Table 1).

When the group was classified according to the cutoff value of Hb <10 g/dl (Table 2), 402 patients (53.8%) were below this limit and 345 (46.2%) above it. Patients with lower hemoglobin levels were older, with higher phosphorus, lower iron and superior EPO requirements.

Table 4: Multivariate analysis. Anemia in HD patients (n=747).

Variable	*OR*	*CI 95%*	*p*
Male gender	1.62	1.17-2.25	**0.003**
Female gender	0.65	0.47-0.90	**0.010**
Diabetes mellitus	1.53	1.06-2.22	**0.022**
Glomerulopathies	0.67	0.32-1.42	0.305
Hypophosphatemia	0.55	0.27-1.10	0.096
Hyperphosphatemia	1.25	0.86-1.83	0.229
Calcium-phosphate product >55mg^2/dl^2	1.20	0.79-1.82	0.388
Iron deficiency	2.36	0.91-6.13	0.076
Absolute iron deficiency	1.18	0.51-2.71	0.689
Serum transferrin <170 mg/dl	0.88	0.47-1.66	0.712
Serum transferrin <200 ng/dl	1.93	1.25-2.98	**0.003**
Serum ferritin >500 ng/dl	1.12	0.59-2.12	0.726
Erythropoietin administration	0.65	0.44-0.95	**0.028**

In the bivariate analysis (Table 3), male gender, diabetes, hyperphosphatemia, higher calcium-phosphate product and iron deficiency were risk factors for Hb under the cutoff limit. Female gender, glomerulopathies, hypophosphatemia, serum ferritin >500 ng/dl and EPO administration were found to be protective factors.

Variables proved to be significant in the univariate analysis were included in the multivariate analysis, this information is shown in (Table 4). Male gender, diabetes and serum ferritin <200ng/dl were independent risk factors for Hb below 10g/dl. Female gender and EPO administration remained as protective factors.

Discussion

The results in this study show a higher frequency of Hb below the recommended value in patients receiving HD at IMSS. Male gender, diabetes and iron deficiency assessed by the serum ferritin levels were the independent risk factors for Hb below the cutoff value.

Anemia is a significant risk factor for cardiovascular comorbidity and cognitive impairment with repercussions on the quality of life [11-20]. For these reasons, it is considered an indicator to optimize treatment and reduce the complications associated with HD. Studies in other populations have acknowledge the presence of anemia in more than 70% of Stage 5 CKD patients [21]. In our study, we found that 94.2% of the patients have anemia according to the definition established by the KDIGO and the WHO. On the other hand, when analyzing the proportion of patients with hemoglobin levels <10 g / dl, as anemia was defined in our study, we identify that 56% of the patients do not meet the hemoglobin target according to the KDIGO guideline recommendations [22]. The GCC-DOPPS (Gulf Cooperation Council - Dialysis Outcomes and Practices Patterns Study) which included 927 patients in HD, reported mean values of Hb in 10.9 g/dl, ferritin 390 ng/dl, transferrin saturation 28.4% and EPO dose of 8667 UI per week [23]. In our population, the average level of Hb was lower (9.7 g/dl), as were the iron-status indicators (ferritin 327 ng/dl, transferrin saturation 25.29%), and higher doses of EPO were used per week (10 097 UI). Regarding the anemia

management, the GCC-DOPPS reported broader prescription of Erythropoiesis Stimulating Agents (ESA), 88 *vs.* 78.8%; higher IV iron dose, 53% *vs.* 12.4%; and lower oral iron use 20% *vs.* 56.8% with respect to our population.

In this study, Diabetes Mellitus (DM) is recognized as a risk factor for Hb beneath the cutoff limit, a value that persisted through the multivariate analysis. Loutradis and cols [24] encountered a higher prevalence of anemia in diabetic patients (47.8% *vs.* 33.2%, p=0.004) and DM was an independent risk factor for the development of anemia in a study with 368 CKD patients: 184 with DM and 184 without DM (OR 2.20, CI 95% 1.19-4.06).

In the DOPPS work conducted with patients in HD, it was found that the probability of attaining Hb level ≥11 g/dl was associated with mineral metabolism. For every 1 mg/dl rise in serum calcium the OR was 1.32, CI 95% 1.25-1.40, p=0.0001, for phosphorus OR 1.08, CI 95%, 1.05-1.11, p=0.0001, while each 100 pg/ml increment in PTH concentration had a protective factor OR 0.96, Ci 95% 0.95-0.98, p=0.0001 [25]. An inverse association was found in a more recent study performed by Boronat and cols with Stage 4 and 5 CKD patients [26]. For each 1mg/dl rise in calcium levels the OR was 0.29, CI 95% 0.16-0.49, p=0.0001, and the presence of anemia was greater with the increasing phosphorus. For each 1 mg/dl increase in phosphorus the OR was 2.19, CI 95% 1.55-3.15, p=0.001. In our study, serum phosphorus >4.5 mg/dl (OR 1.69, CI 95% 1.21-2.28, p=0.001) and calcium phosphate product >55 mg2/dl2 (OR 1.43, CI 95% 1.01-2.03, p=0.04) were recognized as risk factors for Hb below the cutoff value and serum phosphorus <2.5 mg/dl was the only protective factor (OR 0.44, CI 95% 0.23-0.83, p=0.012). Unlike the commented studies, ours could not establish an association between anemia and hyperparathyroidism (OR 1.59, CI 95% 0.81-3.01, p=0.153); nevertheless, it is important to indicate that PTH concentration levels were only available in 22% of patients.

Iron deficiency anemia is a common complication for CKD patients and has been identified as a cause for ESA resistance [27]. We found iron deficiency (OR 1.95, CI 95% 1.38-2.75, p=0.001) as a risk factor for Hb below the cutoff value. Analyzing the iron status abnormalities in an individual manner, ferritin <200 ng/dl was recognized as a risk factor (OR 1.96, CI 95% 1.41-2.72, p=0.001) and levels greater than 500 ng/dl (OR 0.53, CI 95% 0.35-0.79, p=0.002) were considered a protective factor, findings consistent with the current recommendations for iron supplementation in the KDIGO guidelines [22].

A systematic review and meta-analysis performed by Shepshelovich and cols. [28] which included 2369 patients with CKD in stages 3-5 and 818 patients with stage 5 CKD in dialysis treatment (5D) showed the superiority of IV iron use compared to oral iron supplementation to increase hemoglobin levels 1g/dl (RR 1.61, CI 95% 1.39-1.87 for CKD 3-5 and RR 2.12, CI 1.68-2,72 for CKD 5D) according to actual recommendations. In our study, 72.1% of patients had iron deficiency and just 12.4% were managed with IV iron, while 56.8% of patients received treatment with oral supplements. We did not find the variables related to iron metabolism as risk factors for Hb beneath the cutoff value.

The employment of ESA in the management of anemia in CKD patients increases the levels of Hb, diminishes transfusion requirements and decreases morbidity and mortality [29-33]. In our study, the EPO administration was considered a protective factor for Hb below the cutoff limit with an OR 0.57 (CI 95% 0.39-0.82, p=0.002) in the bivariate analysis and it remained as an independent factor after the multivariate analysis (OR 0.65, CI 95% 0.44-0.95, p=0.028).

In the studied population, we identified that 7.8% of the total patients with anemia were macrocytic anemias; however, a limitation of our results is we did not have routine determinations of folate or vitamin B12 levels. In other studies, macrocytic anemia due to folate or vitamin B12 deficiency is around 5% [7]. No benefit was found with folic acid administration (OR 1.10, CI 95% 0.78-1.54, p=0.572) or B-complex vitamins (OR 1.06, CI 95% 0.76-1.48, p=0.696).

Prescription of ACEI and ARB has been associated with anemia in CKD. A meta-analysis from Cheungpasitporn and cols [10] reported a RR of 1.57 (CI 95% 1.40-1.73, I2=17%) for ACEI and a RR of 1.58 (CI 95%, 1.38-1.83, I2=0%) for ARB use [13]. In our study, ACEI (OR 0.54, CI 95% 0.27-1.10, p=0.091) nor ARB (OR 1.03, CI 95% 0.76-1.39, p=0.84) were recognized as risk factors for Hb under the cutoff limit.

It has been previously described that women have lower levels of Hb and hematocrit than men. Physiological differences between genders participate in this variation. Considering different cutoff values to define anemia in each gender, the lower Hb levels in women are inferior to those in men at all CKD stages [34]. In this study we also encountered differences regarding a lower mean Hb in women (9.29 *vs.*10.01 g/dl); despite this, after conducting the multivariate analysis, the female gender was found to be a protective factor (OR 0.65, CI 95% 0.47-0-90, p=0.010) and, consequently, male gender a risk factor (OR 1.62, CI 95% 1.17-2.25, p=0.003) attributed to a better iron status and less mineral-bone metabolism disturbances in women.

Being retrospective, the study has several limitations, essentially due to the unavailability of laboratory tests of variables with known effect over the presence and severity of anemia such as PTH, vitamin B12 and folate values.

Conclusions

The prevalence of anemia in CKD patients receiving HD treatment at our setting is higher than what has been found in other populations. The modifiable causes associated to a lower concentration of Hb were disturbances in mineral-bone metabolism such as hyperphosphatemia and high calcium-phosphate product, as well as abnormalities in the variables related to iron metabolism and reduced usage of EPO. Periodic studies such the one presented here are necessary to detect improvement opportunities in the quality of care to decrease morbidity and mortality in HD patients.

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